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BRITISH MEDICAL BULLETIN

March 1943 Vol. 1, No. 1

The object of this Bulletin is to provide a guide to medical science and thought in Britain, and it consists mainly of summaries of a representative selection of British papers on subjects of medical interest. Any material appearing in the Bulletin may be published without fee, but acknowledgement of the source, by addition of the initial letters BMB followed by the serial numbers of the items selected, would be appreciated. The Bulletin is not distributed generally to the medical profession.

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FURTHER DATA ABOUT THE CIRCULATION AND ABOUT THE CARDIO-VASCULAR SYSTEM BEFORE AND JUST AFTER BIRTH

by A. E. Barclay, K. J. Franklin, and M. M. L. Prichard, *British Journal of Radiology*, **15**, 249–256, September, 1942

The observations reported in the present paper from the *Nuffield Institute for Medical Research*, Oxford, supplement earlier reports of an investigation which the authors carried out in collaboration with Sir Joseph Barcroft, the distinguished Cambridge physiologist, Dr. D. H. Barron of the School of Anatomy at Cambridge, and others. These studies furnish a peculiarly interesting example of the value of an advanced radiological technique in elucidating problems which have exercised the imaginations of anatomists and physiologists for many centuries.

The object of the earlier investigations was to discover, by the use of direct and indirect cineradiography (Barclay, Franklin & Prichard, 1940) with intravascular injection of radio-opaque media, the time and manner of closure of the *ductus arteriosus*, using the mature fœtal lamb as the experimental animal. After an initial failure, the ductus arteriosus was identified by analysis of the cine records and times were obtained for its functional closure (Barclay, Barcroft, Barron & Franklin, 1939; Barclay, Barcroft, Barron, Franklin & Prichard, 1941). The authors also obtained times for the closure of the *foramen ovale* and made a film of the contractions of its " valve."

The most significant feature of these investigations, however, was that it became apparent during the analysis of the cineradiographic films that the authors had, for the first time in history, obtained direct records of the circulation in the intact fœtus. These records, commencing in some cases less than 30 seconds from delivery, showed that all the superior-anterior caval blood went to the right atrium and right ventricle, while the inferior-posterior caval blood went mainly, via the foramen ovale, to the left atrium and left ventricle, and to a lesser extent to the right side of the heart. From the right ventricle the blood passed to the pulmonary trunk [illegible] thence to the pulmonary arteries and via the ductus [illegible] to the descending aorta. From the left ventricle the blood passed to the first part of the aorta from which some of it went to the coronary and brachio-cephalic arteries, while the remainder continued its course to unite with that flowing into the descending aorta, via the ductus arteriosus, from the right ventricle. There were also records showing the umbilical venous inflow into the liver, but the various vessels within that organ were not identified in detail.

At this stage the war interrupted the collaboration of the present authors with their Cambridge colleagues, and they engaged in an historical study of the literature from the time of Galen onwards upon the fœtal cardio-vascular system, and from Harvey's time onwards upon the fœtal circulation (Franklin, 1941a, 1941b; Amoroso, Barclay, Franklin & Prichard, 1942). This study provided valuable material for a further series of experiments and dissections.

A later series of cineradiographic records confirmed all previous findings, provided new information on the afferent and efferent venous circulation in the liver, and suggested the presence of a sphincter mechanism at the beginning of the *ductus venosus* (Barclay, Franklin & Prichard, 1942). All fœtuses were fixed post mortem and provided the basis for an anatomical study of the cardio-vascular system (Franklin, Barclay & Prichard, 1940).

The authors then decided to investigate the comparative anatomy of all available eutherian (placental) fœtuses (these included such rarities as elephant, gorilla and whale). The result of this comparative anatomical study was that it was found to be impossible to describe structures correctly in terms of function, as experimentally determined on the fœtal lamb, by the use of the current terminology.

A new nomenclature was therefore formulated (Amoroso, Franklin & Prichard, 1941; Amoroso, Barclay, Franklin & Prichard, 1942) which included the following terms:

1. *Inferior-posterior caval channel*, bifurcating within the heart on a *dividing ridge* or *crista dividens* into *left* and *right terminal divisions*, the former (the " foramen ovale " in one of its connotations) being composed of a *fixed portion* and a *free* or *apposable portion* (the so-called " valve of the foramen ovale ").

2. *Superior-anterior caval channel*, separated from the right terminal division of the inferior-posterior caval channel by a *crista interveniens* (tuberculum intervenosum Loweri).

It was shown, *inter alia*, that—

(*a*) the dividing ridge, on which the inferior-posterior caval channel bifurcates, is a prominent feature in every fœtal heart examined (Franklin, Amoroso, Barclay & Prichard, 1942).

(*b*) An appreciation of the bifurcation of the inferior-posterior caval channel is essential for the proper understanding of the blood flow into the fœtal heart.

(*c*) The right group of pulmonary vein entries shares with the left terminal division of the posterior caval channel an opening into the left atrium, so the inflow from the former source can increase only at the expense of the inflow from the latter source (Amoroso, Barclay, Franklin & Prichard, 1942). This may be of importance in regard to the post-natal functional closure of the " foramen ovale " (the *left terminal division* of the *inferior-posterior caval channel* in the suggested new nomenclature).

(*d*) The ductus venosus " sphincter " is present in various mammals, including man (Barclay, Franklin & Prichard, 1942).

The main findings recorded in the present and latest paper may be summarized as follows:

1. Recording with the fœtus in the dorsal position, although much less satisfactory than in the lateral position, showed the division of the posterior caval stream into its two terminal divisions and provided certain further data about the liver.

2. The circulation in fœtuses of 100 days and slightly over was very similar to that in mature (147-day) fœtuses.

3. Comparison of the cardio-vascular system of early fœtuses with that of mature fœtuses was of interest mainly in connection with the liver, which furnishes a progressively smaller proportion of the body weight, and moves more and more to the right side of the body from the 69th day to fœtal maturity.

4. In two fœtuses, the only ones available for this particular study, the ductus venosus became functionally impervious between 5 and 25 minutes from ligation or rupture of the umbilical cord. Factors possibly concerned in the closure are the onset of respiration, the reduction of the placental circulation, and the detachment of the placenta and rupture of the umbilical cord. It was shown that closure of the ductus venosus can occur after delivery of the fœtus when the placental circulation is still intact and respiration is deliberately prevented (by covering the muzzle of the fœtus with a " nose-bag " full of amniotic fluid). It was therefore evident that the act of delivery alone, possibly with some restriction of the placental circulation due to cooling or other factors, may be followed by partial or total closure of the ductus venosus.

5. In the mature fœtus the umbilical vein supplies 60–70% of the total liver mass, the remainder being supplied by the portal vein.

6. Evidence is given suggesting that the umbilical vessels are particularly contractile where such contractility would appear to be most useful, *i.e.* at the level of the umbilicus itself.

The authors believe that the investigations reported in this and previous papers provide the basis for a reasonably accurate account of the cardio-vascular system and circulation in the mature fœtus, and explain to a considerable extent the changes which occur shortly after parturition.

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2

THE INFLUENCE OF ATROPINE UPON COMPLETE HEART BLOCK, TRANSIENT AND INTERMITTENT

by R. A. Miller, *Edinburgh Medical Journal*, 49, 757–765, December, 1942

In four cases of transient or intermittent complete heart block $\frac{1}{300}$ grain (about 2 mg.) atropine sulphate given intravenously produced normal sinus rhythm. In a fifth case atropine failed to abolish transient complete heart block produced by digitalis therapy. In this particular case normal sinus rhythm appeared spontaneously after digitalis therapy had ceased for eleven days.

On correlating these results with those previously recorded in the literature, it can be stated that complete heart block of type I or type II may or may not be abolished by atropine. The facility with which the drug brings about the transformation does not depend so much on the ætiology of the disorder as on the extent and severity of the lesion. Tachycardia or digitalisation may also modify a reaction, the former accentuating defective conduction in type II heart block, while digitalis therapy sometimes impairs the conduction of the bundle of His to such an extent that atropine fails to abolish the complete heart block.

The manner in which complete heart block passes to sinus rhythm or *vice versa* was studied in one case with the rare type of intermittent block, and it may be concluded that a 3 : 1 auriculo-ventricular response usually develops either before or following complete block. Rarely a 4 : 1 response was recorded when the auricular rate rose to 138 beats per minute. In one instance the first step in the passage from complete heart block to sinus rhythm was effected by every idioventricular beat alternating with a driven sino-auricular beat, so that an inconspicuous type of coupling of ventricular complexes was observed. In another case the transition from complete block was somewhat similar in that the frequency of auricular impulses conducted to the ventricles increased after atropine administration but in a non-rhythmical fashion.

3

ARTERIAL SPASM

by J. M. Barnes and J. Trueta, *The British Journal of Surgery*, 30, 74–79, July, 1942

The object of this paper is to report investigations on the experimental production of arterial spasm in the limbs of rabbits. The authors, from the *Sir William Dunn School of Pathology* and the *Nuffield Department of Orthopædic Surgery* at Oxford, began this work in an attempt to find an explanation for some of the changes seen in the limbs in cases of *crush syndrome*—a condition seen in air-raid casualties in which crushing injuries of the limbs are associated with anuria (see *Note*). In some of these cases there were signs of impairment of the circulation of the injured limb without evidence of gross vascular damage. A possible explanation was that the initial injuries had caused an arterial spasm which persisted after the release of the victim. The authors therefore decided to determine experimentally whether the application of an inelastic tourniquet would produce a disturbance of the vascular supply of a limb which would persist after the release of the constriction.

The experiments were performed on rabbits. A piece of wire protected by rubber was tied tightly round one leg at the level of the groin. It was released after 4½ hours, and arteriograms, using a sodium iodide solution as contrast medium, were taken at various intervals up to 72 hours after the release of the tourniquet. These showed that the main artery and the collateral vessels of the affected limb were still in spasm. There was also spasm of the main artery of the opposite uninjured limb.

In another group of animals the lumbar sympathetic nerves were infiltrated with 2% procaine solution after removing the tourniquet. Arteriograms taken 30 minutes later showed that the vascular spasm still persisted. In a third group of animals the lumbar sympathetic nerves were removed immediately after the release of the tourniquet. Arteriograms taken 24 hours later showed slight spasm of the main artery, but there was an excellent collateral circulation. Unlike the legs of the animals of the first two groups, the legs of these animals bled profusely when the muscles were incised.

Two animals were killed 14 and 21 days after the removal of the tourniquet, and histological examination of the muscles of the leg showed the characteristic microscopical changes of Volkmann's ischæmic contracture.

The authors discuss the significance of their findings, and emphasise the following points:

1. Spasm of the arteries may persist for at least 3 days after the release of the tourniquet.
2. The spasm may also affect the main artery of the uninjured limb.
3. Infiltration of the sympathetic nerves with procaine did not abolish the vascular spasm.
4. Removal of the sympathetic nerves greatly improved the collateral circulation.
5. Persistent arterial spasm resulted in the development of a condition of the muscles histologically similar to that seen in Volkmann's ischæmic contracture.

NOTE: *Crush syndrome* is discussed in the following papers:

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4

RETENTION OF INJECTED SERUM IN THE CIRCULATION

by E. P. Sharpey-Schafer and J. Wallace, *Lancet*, 1, 699–701, 13/6/42

In recent years, solutions of human plasma proteins have been extensively used in the treatment of casualties. The present authors report investigations carried out in the Department of Medicine of the *British Postgraduate Medical School* (London) and designed to throw further light on the behaviour of such solutions in the circulation.

The degree of retention of injected serum was assessed by serial hæmoglobin determinations in subjects without cardiovascular disease. 700 to 2100 cm^3. of normal strength serum was given to 13 subjects at rates between 50 and 150 cm^3. per minute. In 5 subjects initial dilution of hæmoglobin was small or non-existent, indicating that injected fluid had left the circulation rapidly. In the others, initial dilution was up to 25%, but in all a return to the initial level of hæmoglobin took place over minutes or hours.

Nine subjects were given 200 to 615 cm^3. serum of 4 times the normal concentration. Several of these showed little or no initial dilution of hæmoglobin, and as there was no change in plasma proteins, protein as well as water and salts must have left the circulation rapidly. These subjects had normal blood volumes.

A striking difference was, however, found in subjects with acutely reduced blood volumes. In 6 subjects 700 to 1100 cm^3. of blood was rapidly removed and serum was injected in similar quantities to those used in the previous experiments. Initial hæmodilution was great (up to 32%) and was maintained up to 48 hours, indicating that serum injected after acute reduction of blood volume is retained in the circulation. When saline was substituted for serum after bleeding, it was not retained in the circulation.

These results show that in the normal individual injected serum is lost, sooner or later, from the rapidly circulating blood-stream. Large quantities of protein may also leave the circulation rapidly. When, however, an individual is suffering from acute blood loss, injected serum is largely retained in the circulation. Saline solution, as is well known, is not retained.

5

CIRCULATORY OVERLOADING FOLLOWING RAPID INTRAVENOUS INJECTIONS

by E. P. Sharpey-Schafer and J. Wallace, *British Medical Journal*, **2**, 304–308, 12/9/42

There is a wide variation in recommendations by different authorities on the amounts of serum or blood which should be administered and the rate at which they should be injected. The danger of overloading the circulation has been stressed, and it was shown by Bayliss & Starling in 1894 that rapid injection of crystalloid solutions or blood caused a rise of venous pressure. In view of the relatively inadequate data available for man, the present authors, working at the *British Postgraduate Medical School* (London), carried out the investigation reported in this paper.

Cardiovascular measurements were made in subjects without circulatory disease after rapid injections of saline, serum and blood. One group had normal blood volumes and in the other group the blood volume was acutely reduced by venesection. In those with normal blood volumes, up to 2000 cm^3. of saline solution, serum or blood were given at rates of from 54 to 168 cm^3. per minute. It was observed that the venous pressure began to rise after about 1000 cm^3. had been given and reached a maximum (up to 11 cm. of water) at the end of the injection. When the injection ceased the venous pressure fell rapidly to normal except in one subject given blood.

The rise of venous pressure could be correlated with the degree of retention of injected serum in the circulation as judged by the fall in hæmoglobin, and it was found that there was a statistically significant relationship between the rise of venous pressure and fall of hæmoglobin. Immediately after injection the vital capacity of the lungs was diminished by an average of 470 cm^3. in 6 subjects, but there was no evidence of pulmonary œdema. X-rays showed that the diastolic size of the heart was increased by an average of 15·8% in 5 subjects, and there was enlargement of the pulmonary arteries and increased density of the vascular markings in the lung fields. The electrocardiogram showed evidence of slight right heart stress in 4 of 12 subjects. In spite of the rise of venous pressure, 9 subjects showed no change in heart rate while 6 showed an increase. Symptoms were unimportant. Similar experiments performed directly after a large reduction of blood volume (1000 cm^3.) by venesection showed no rise of venous pressure from injection of serum or saline solution.

The authors conclude that the degree of overloading involved by the injection into the circulation of volumes such as were used in their experiments is rapidly accommodated by the normal individual.

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6

PLASMA PROTEIN CONCENTRATION AFTER HÆMORRHAGE

by J. Beattie and H. B. Collard, *British Medical Journal*, **2**, 301–304, 12/9/42

This paper from the *Bernhard Baron Research Laboratories* of the Royal College of Surgeons of England reports the results of an experimental investigation on hæmorrhage. After hæmorrhage in man and experimental animals, fluid enters the blood stream and restores the blood volume. This occurs rapidly in cats and less rapidly in dogs and man. With the entry of this fluid the hæmoglobin concentration shows a progressive fall which ceases at or about the time when the pre-hæmorrhage blood volume is restored. The time taken to restore the blood volume may be as short as ½ to 2 hours in cats and from about 4 to 90 hours in man.

The amount of blood withdrawn in the present experiments was about 20% of the initial blood volume. The time taken to complete the removal of blood does not influence the time taken to restore the blood volume. Observations were made on changes in the hæmoglobin and plasma protein concentrations in anæsthetised cats following such hæmorrhages. It was found that there was evidence of movement of plasma proteins into the blood stream which were not parallel to the movement of fluid as judged by the fall in hæmoglobin concentration. It appeared, therefore, that the migration of plasma proteins was independent of the inflow of fluid and that the fluid and the proteins came from different sources.

An analysis of data provided by Wallace & Sharpey-Schafer (1941) and based on similar experiments on unanæsthetised human subjects showed that the same phenomena occurred. The rate of entry of plasma protein into the circulation in man was, however, sufficient in several experiments to maintain a constant plasma protein concentration. The present authors reach the conclusion that the inflow of plasma proteins into the blood after hæmorrhage depends more on the state of the plasma protein stores than on any other factor, and that this conclusion applies both to man and animals.

If the blood removed from cats is re-injected some time after hæmorrhage, the blood volume shows an increase above the pre-hæmorrhage value. This is due to the fact that the process of restoration of blood volume had progressed considerably before the re-injection of blood. This excessive blood volume is rapidly reduced, as may be seen by the rapid rise in hæmoglobin concentration due to the outflow of fluid from the circulation. The plasma protein concentration, however, does not show a parallel rise. This can only mean that plasma proteins have also left the circulation.

When plasma was transfused after a previous hæmorrhage, the hæmoglobin concentration fell, as might be expected. There was, however, in these animals evidence that plasma proteins moved out of the circulation within an hour after plasma transfusion. The plasma protein concentrations in such animals tended to return to the pre-hæmorrhage level. The administration of repeated plasma transfusion leads eventually to a state in which the concentration of plasma proteins is raised much above its pre-hæmorrhage level. This has been taken to indicate that the restoration of the normal blood volume from the excessive value after plasma transfusion can still be effected, but the excess protein concentration seen in such animals may indicate a state of repletion of plasma protein stores.

These animal experiments indicate that the restoration of blood volume is a process independent of the mechanism involved in the maintenance of a constant concentration of plasma proteins. The factors which are concerned in the restoration of blood volume are as yet not fully understood. In the maintenance of a constant plasma protein concentration after hæmorrhage and after blood and plasma transfusions it would appear that the amount of protein available in tissue cells for transfer into the blood stream as plasma protein is a major factor.

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7

CAPILLARY FRAGILITY (RESISTANCE): NEGATIVE- AND POSITIVE-PRESSURE TEST COMPARED

by G. H. Bell, S. Lazarus, H. N. Munro and H. Scarborough, *Lancet*, **2**, 536–538, 7/11/42

The state of the capillary walls is of special interest in relation to hæmorrhagic diseases and certain vitamin deficiencies. Capillaries can be made to rupture by increase of internal pressure (positive pressure) produced by venous congestion, or by suction (negative pressure) applied to the capillary walls through the skin.

It is usually assumed that the methods based on these two principles give directly comparable results, but there are reasons for doubting this assumption. The present authors, working at the Institute of Physiology of *Glasgow University*, and the Clinical Laboratories of *Edinburgh Royal Infirmary*, have compared the results obtained with both methods. Using a positive pressure method, there was no evidence that vitamin-P preparations had the effect of increasing capillary resistance. In another series of experiments in which negative pressure was used, there was evidence of an increase of capillary strength after the administration of vitamin-P preparations.

Before assuming that the difference in results was due to differences in clinical material, the authors decided to compare the two tests directly at the same session on a group of 142 students. Each of the tests was found to be consistent within itself, and there was a high correlation between the

readings in different skin areas when the same test was applied. However, when the results of one test were compared with the results of the other, the correlation was very low and not always statistically significant.

The authors therefore conclude that the results of the negative and positive pressure tests are not comparable. This investigation did not provide any evidence as to which of the two methods of measuring capillary strength is to be preferred.

8

THE CLINICAL SIGNIFICANCE OF THE Rh FACTOR

by K. E. Boorman, B. E. Dodd and P. L. Mollison, *British Medical Journal*, **2**, 535–538 and 569–572, 7/11/42 and 14/11/42

Much interest has lately been shown in the recently discovered Rh factor (or Rh antigen) in blood. The presence of this factor in certain human erythrocytes was first discovered by testing samples with anti-rhesus sera, prepared by injecting the blood of rhesus monkeys into rabbits. It was found that 85% of human bloods, irrespective of group, were agglutinated, whereas 15% were not. The former are termed "Rh-positive" and the latter "Rh-negative." Persons whose erythrocytes are Rh-negative are capable, under certain circumstances, of forming an antibody which reacts with the Rh antigen. This may occur after transfusions of Rh-positive blood or, probably more commonly, when a woman (herself Rh-negative) becomes pregnant with a baby whose erythrocytes are Rh-positive.

Wiener & Peters (1940) first demonstrated the practical importance of the Rh factor by describing hæmolytic reactions after transfusion of "compatible" blood in 3 Rh-negative patients. The blood used for transfusion was shown to be Rh-positive. Levine, Burnham, Katzin & Vogel (1941) concluded from an investigation of 153 cases of *erythroblastosis fœtalis* that the cause of the condition in most cases was iso-immunisation of an Rh-negative mother to the Rh-antigen contained in her (Rh-positive) fœtus, with subsequent passage of the immune anti-Rh agglutinin from the maternal to the fœtal circulation.

In the present paper, the authors have sought to confirm many of the observations made by other investigators and also to present some new findings. In every case of erythroblastosis examined the serum of the mother was found to contain an immune agglutinin which was incompatible with the infant's erythrocytes. In 44 out of 48 cases the agglutinin was anti-Rh. In the remaining 4 cases it was either anti-A or anti-B. Because of this latter finding the authors consider that the anti-A and the anti-B agglutinins are capable of causing destruction of the infant's erythrocytes in a certain number of cases and thus, in some instances, of being the main causative factor of the erythroblastosis. The finding of weak Rh antibodies in the sera of the mothers of some babies with "physiological jaundice" supports the idea that there is no definite distinction, from the clinical point of view, between mild and severe jaundice of the newborn.

At the present time, if serological tests are used as an aid in the diagnosis of doubtful cases of erythroblastosis, compatibility of the mother's serum with the infant's erythrocytes may be regarded as a strong point against the diagnosis, provided that the mother's serum is examined by a sensitive technique between 7 and 21 days after delivery. On the other hand, if the mother's erythrocytes are shown to be Rh-negative and her serum is found to contain anti-Rh agglutinins, the diagnosis is strongly supported.

The authors believe that a change in the method of selection of blood donors in certain cases is urgently needed. This applies particularly in the case of transfusion of recently delivered women and, above all, whenever there is any suspicion that the infant is affected with erythroblastosis or when there is any previous history of the birth of jaundiced babies or of stillbirths without obvious cause.

At the same time, a modification of the present method of testing for compatibility between the bloods of donor and recipient must be made. The authors describe in detail methods for carrying out such tests and discuss compromise procedures for cases in which there are no facilities for making these tests. They recommend that every blood bank should take steps to establish a panel of group O Rh-negative donors whose blood will be available, first, for the transfusion of the cases referred to above, and, secondly, for use as a routine in the transfusion of infants affected with erythroblastosis (when transfusion is required).

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9

THE SEDIMENTATION RATE AND THE SEDIMENTIN INDEX

by B. L. Della Vida, *British Medical Journal*, **2**, 278–280, 5/9/42

For estimations of the sedimentation rate of the red cells to be comparable it is essential that they be performed by an identical technique and expressed in the same manner. The rate of sedimentation of the red cells depends on a function of the plasma which, as suggested by Day (1940), may be spoken of as *sedimentin*.

Factors influencing the rate of sedimentation are : (*a*) size and position of tubes, (*b*) erythrocyte volume, (*c*) anticoagulants used, (*d*) time elapsing after collection of sample, (*e*) circumambient temperature, (*f*) size of the erythrocytes (the variations due to this factor are not significant).

The sedimentation rate should be expressed as mm. fall per minute during the period of constant fall. The measurement of the activity of the sedimentin is given by the logarithm of the figure expressing the rate of fall over 100 minutes calculated on the basis of the constant fall per minute.

The author recommends the following technique:

1. Five cm^3. of blood are withdrawn by venipuncture into a dry mixture of 4 mg. of potassium and 6 mg. ammonium oxalate.
2. The estimation is made within four hours of withdrawal of the blood. If this is not possible the plasma may be separated and used with fresh washed erythrocytes.
3. A tube giving a blood column of 200 mm. in height and at least 2·5 mm. in diameter is used. This must be set up strictly vertically.
4. Only the rate of fall during the period of constant fall is considered in the expression of results.
5. Correction is made for anæmia. This may most conveniently be done by making use of the Sedimentin Index of Day according to the formulæ:

$$\textit{Sedimentin Index} = \log.(\text{Sedimentation Rate} \times 100)\,\frac{55}{100 - \text{Corpuscular Volume}}$$

and

$$\textit{Sedimentation Rate}\ (\text{corrected}) = \frac{\text{antilog. Sedimentin Index}}{100}$$

REFERENCE

Day, G. (1940), *Lancet*, **1**, 1160.

10

MAXIMAL RESPONSE TO LIVER THERAPY IN PERNICIOUS ANÆMIA

by B. L. Della Vida, *Lancet*, **2**, 275–278, 5/9/42

There are wide differences in the amounts of liver extracts used in the treatment of pernicious anæmia. Before this unsatisfactory situation can be remedied, it is necessary to establish criteria of potency of liver extracts. With this object in view, the author has collected data from the records of the Pathological Department of the *Royal Hospital*, Wolverhampton.

The response to successful liver treatment in patients suffering from pernicious anæmia is revealed by a reticulocyte crisis on or about the fifth day, and by increase in erythrocytes. These expected values can be calculated from the erythrocyte count before treatment according to the formulæ proposed by Riddle (1940):

$$\text{Expected reticulocyte percentage} = \frac{0{\cdot}73 - 0{\cdot}2\ \text{Eo}}{0{\cdot}73 + 0{\cdot}8\ \text{Eo}}$$

and

$$\text{Expected weekly erythrocyte increase} = 0{\cdot}78 - 0{\cdot}174\ \text{Eo}$$

where Eo represents the erythrocyte count before treatment.

From the data obtained in about 125 cases of pernicious anæmia in the author's series, an analytical survey has been made in the light of the above formulæ, and the following conclusions have been reached.

The reticulocyte response does not give an accurate indication of the effectiveness of liver treatment and is therefore not reliable by itself as a means of assessing the potency of liver extracts. The increase in erythrocytes is found to be maximal in the first two or three weeks of treatment and bears an inverse relationship to the erythrocyte count before treatment.

The cases reviewed have been found to fall into three distinct groups which have been labelled "unsatisfactory," "average" and "satisfactory." For each group a mathematical equation has been calculated expressing the relationship between the initial erythrocyte count and the weekly increment.

The equation obtained from the "average" group, $I = 0{\cdot}93 - 0{\cdot}214\ Eo$ (where I is the average weekly increase in red cells during the first two weeks of treatment, and Eo is the red cell count before treatment), has been found to express a satisfactory response to treatment and is proposed as the standard equation for the assessment of the potency of liver extracts.

A large proportion of the cases have been found to give a response to treatment better than was to be expected from previously published formulæ.

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11

ELECTRO - ENCEPHALOGRAPHIC STUDIES OF PSYCHOPATHIC PERSONALITIES

by D. Hill and D. Watterson, *Journal of Neurology and Psychiatry*, **5**, 47–65, January and April, 1942

The classification of psychopathic personality used in this paper, which was read before the Psychiatric Section of the Royal Society of Medicine (London), is that of Henderson (1939), except that no creative psychopaths (brilliant but unstable eccentrics) were examined. The case material, which was largely drawn from a military mental hospital and an *Emergency Medical Service* (Ministry of Health) neurosis centre, consisted of 93 *predominantly aggressive* psychopaths and 58 *predominantly inadequate* psychopaths. These were compared with 52 controls who were doctors, hospital staff, and Army nurses.

The apparatus used was a 3-channel Grass ink-writing oscillograph. The amplifiers were linear from 3 to 50 cycles, and the high-frequency filters were kept at position "3" (as used by other workers with this standard apparatus). The electrodes, which were made of silver tube covered with a saline pad, were held to the head by an open mesh rubber cap (Walter, 1937). Bipolar electrode placement was used in every case, usually with four electrodes on widely separated areas of the head, two on each hemisphere. Whenever accurate localisation of an abnormality was attempted, the method of Gibbs & Gibbs (1941) was used. Each record was taken for 20–25 minutes, including 3 minutes of voluntary hyperventilation.

Criteria of Abnormality

1. A dominant rhythm with a frequency of less than eight per second.
2. Bursts of two or more waves with a frequency less than seven per second and a voltage more than half that of the dominant rhythm.
3. A series of waves with a frequency of 14 or more, rising in voltage to over half that of the dominant rhythm.
4. Spike and wave complexes.
5. Single random waves at 6 per second or less, with a voltage equal to or more than that of the dominant rhythm, provided such waves are repeated from the same cortical area.
6. Hyperventilation
   - (*a*) spike and wave complexes;
   - (*b*) all waves with a frequency of 2–3 per second and a voltage over 100 microvolts which persist either in bursts for a short period, or continuously for more than 20 seconds after cessation of hyperventilation.

In any doubtful case the patient was re-examined after at least four hours' starvation.

Results

Jasper, Solomon & Bradley (1938) and Lindsley & Cutts (1940) have demonstrated electroencephalographic abnormalities in behaviour problem children, and Putnam & Merritt (1941) have shown an increase of dysrhythmia, with episodic behaviour disorder in epileptic adults, but such behaviour, *without epilepsy but with dysrhythmia*, has not so far been demonstrated in adults.

Of the 151 patients in the present series, 48% had abnormal electroencephalograms; 13% were abnormal *only* in the resting record, 15% *only* after hyperventilation, and 20% showed the double abnormality. In the control group of 52 individuals, 15% had abnormal electroencephalograms; 6 were abnormal in the resting record *only* and 2 showed the double abnormality; none was abnormal on hyperventilation *only*. A psychiatric examination of the controls by questionnaires and personal interview demonstrated that all except one of the abnormal controls had an abnormal degree of irritability, aggressiveness, and impulsiveness in their personalities.

Of the aggressive psychopaths, 65% had abnormal electroencephalograms and the more aggressive the patient, the more likely was the electroencephalogram to be abnormal. 32% of the inadequate psychopaths had abnormal electroencephalograms. Simple delinquency and sex perversion were not associated with a greater percentage of electroencephalographic abnormality than the controls. When epilepsy was associated with aggressive psychopathy the electroencephalographic abnormality rose to 81%.

Examination of the influence of factors in the patients' histories likely to change the electroencephalogram showed that while head injury may account for a percentage of the abnormality among inadequate psychopaths, there was no evidence that it was responsible in the same degree among aggressive psychopaths. This was surprising in view of the fact that head injury can produce aggressive personality change and also electroencephalographic abnormality. In the family histories, aggressive bad temper was found nearly three times as frequently among the first-degree relatives of aggressive psychopaths as among those of the inadequate group. Epilepsy was not found to the same extent. The presence of epileptoid conditions in the parents and siblings did not increase the chance of an abnormal electroencephalogram in either group of patients.

Type of Abnormality

The most characteristic abnormality of the resting record was a 4–6 per second rhythm, with a voltage slightly less than that of the dominant rhythm. The waves were seen in bursts of three to six at a time. In some cases this abnormal rhythm had a voltage greater than that of the dominant, and in many it was equal to it. In 11 out of 51 abnormal resting records, rhythms of 3 per second were seen and these were comparable to Walter's delta foci in epileptics. In 25 cases, the rhythms were found in the post-central regions and in 26 cases the rhythms were apparently bilaterally synchronous. The hyperventilation response is regarded as a non-specific abnormality, liable to occur in any abnormal brain. Seventy-seven per cent. of the aggressive dysrhythmics and 75% of the inadequate dysrhythmics showed this abnormality.

The authors point out that the electroencephalographic abnormalities might have resulted from head injury, either at birth or later, but consider that the tendency to bilateral synchronous discharge, the paroxysmal quality of the latter, and the absence of generalised irregularity are against this explanation. The abnormalities were similar to those found in epileptics, yet only a very small percentage of the patients had actually had fits. The authors favour the view of a constitutional cortical immaturity. Such a view agrees with psychiatric, biological, and social conceptions of psychopathic personality. The similarity between the aggressive behaviour of psychopaths and the normal bad-temper response to frustration in young children on the one hand, and the similarity between the electroencephalograms of aggressive psychopaths and those of young normal children on the other, suggests that the electroencephalographic abnormality in psychopaths is produced by a failure of development in the central nervous system.

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12

OBSERVATIONS IN HYPOGLYCÆMIA: IV. BODY TEMPERATURE AND COMA

by W. Mayer-Gross and F. Berliner, *The Journal of Mental Science*, 88, 419–427, July, 1942

This paper reports one of a series of investigations on the phenomena of hypoglycæmia carried out at the Department of Clinical Research of the *Crichton Royal Hospital*, Dumfries (Scotland). Previous papers have been on: "I. Oral and Facial Movements" (Mayer-Gross, 1941); "II. Blood Sugar and Consciousness" (Mayer-Gross & Berliner, 1941); and "III. Cerebrospinal Fluid Sugar and Coma" (Mayer-Gross & Berliner, 1942).

The authors now record their observations on the fluctuations of body temperature during insulin treatment of psychoses and the correlation of such fluctuations with the clinical signs of hypoglycæmia. Fall of body temperature during hypoglycæmic coma has previously been observed by many workers. It is important as a possible indicator of hypothalamic activity during the insulin treatment of psychoses and may throw light on the factors operative in this treatment.

The rectal temperature was recorded in 11 male patients on 129 days by means of a thermocouple connected with an electric thermometer during the various stages of hypoglycæmia, including mild motor excitation and epileptiform convulsions. Days without coma served as controls. The room temperature varied between 15° C. and 20° C., and was highest at about 11.0 a.m. when the patients were in coma.

Usually the temperature remained level for about 2 hours after the insulin injection. It began to rise when the first hypoglycæmic symptoms (perspiration, flushing, oral movements, restlessness and drowsiness) appeared. After half to one hour the temperature began to fall and the symptoms became more marked. Then the temperature sank below its initial level, and clinical signs of coma appeared during the decline. The latter continued until coma was interrupted by the administration of sugar.

While the patient regained consciousness the temperature rose slowly to normal. In a typical case the temperature rose in the precomatose stage from 36° C. to 36·4° C. After about 30 minutes it began to fall and reached about 35° C. before coma was interrupted. This sequence represents the typical temperature curve, and the number of atypical curves was small. The degree of temperature variation differed considerably between different patients, but it tended to follow a constant pattern in the same patient on different days.

Profuse perspiration was present during the rise as well as during the fall of temperature. On some occasions the greatest restlessness coincided with the maximal temperature rise, but usually twitching and other forms of hyperkinesis increased even more during the decline of the temperature curve. In some cases coma started almost simultaneously with the fall of temperature, and in others the decline of the temperature curve preceded coma by 15–30 minutes. If the coma became deeper after a nasal feed, the curve declined again after a short flat period. Intravenous glucose given until the patient was conscious always produced an immediate rise of temperature. Synchronism of temperature rise and return of consciousness was complete. The temperature was an objective indicator of the end of coma, but had no clear relation to the beginning of coma.

Simultaneous control of blood-sugar and temperature showed that the rise of blood-sugar was not so closely correlated to the return of consciousness as was the upward turn of the temperature curve. In spite of high blood-sugar findings after nasal feeding, the temperature remained low until the patient regained consciousness. Adrenaline injections influenced the temperature only if the patient was awakened by the injection.

Both the precomatose rise of temperature and the reduction in the degree of coma can be explained by peripheral mechanisms. The former may be caused by muscular exertion and by secretion of adrenaline into the blood stream, of which there are many clinical signs in hypoglycæmia. Its presumed purpose is to combat the parasympathetic effect of insulin. Later this compensatory action fails because of the exhaustion of the body's carbohydrate reserve. Heat production then becomes impossible, the body temperature falls and the parasympathetic symptoms become predominant.

However, the close temporal relationship between temperature and state of consciousness, as demonstrated in the authors' observations, are in favour of a central disturbance of heat regulation, similar to that in hypothalamic tumours and possibly also to the temperature fall in normal sleep. The widely divergent views on central autonomic disturbances in schizophrenia render a conclusive theory of the effect of hypoglycæmia impossible; but the temperature observations confirm the strong stimulating influence of hypoglycæmia on both divisions of the autonomic nervous system, peripherally and centrally.

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13

THE OCCURRENCE OF THE GRASPING REFLEX IN THE POST-CONVULSIVE STAGE OF ELECTRICALLY INDUCED SEIZURES AND ITS BEHAVIOUR IN VARIOUS MENTAL DISEASES

by F. F. Kino and F. T. Thorpe, *Journal of Mental Science*, 88, 541–544, October, 1942

Observations made during convulsions electrically induced for therapeutic purposes provide a unique opportunity for the study of convulsive states and their accompanying phenomena in man. The present authors have studied these phenomena in 100 cases treated at *West Riding Mental Hospital*, Sheffield. The cases represented an average sample of a mental hospital population.

Among the many interesting manifestations of the post-convulsive stage was a grasping reflex. This reflex has previously been observed only in certain structural disorders, such as cerebral tumour, of the frontal lobes of the brain. The reflex occurred as a transient phenomenon elicited from 3 to 6 minutes after the onset of the convulsion, and it lasted for 1 to 3 minutes. The optimum stimulus for its appearance was found to be 100 volts for 0·5 second applied to the pre-frontal cortex through the temples.

The three components of the reflex as described by Walshe & Hunt (1936)—reflex tonic grasping, forced grasping and groping—were all found in these cases, but could be elicited only during the period of unconsciousness following the convulsion. Reflex tonic grasping (termed "clutching") was the prevailing component stimulated by pulling of the flexors of the fingers.

In the authors' series of cases, it was found that patients with manic-depressive psychosis and involutional melancholia reacted invariably with a vigorous grasping reflex, while the reflex was usually absent or irregular in the acute schizophrenics. Further observations are necessary before any definite conclusions can be drawn from these findings.

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14

MINERAL METABOLISM ON DEPHYTINIZED BREAD

by R. A. McCance and E. M. Widdowson, *Journal of Physiology*, **101**, 304–313, 30/11/42

Although Mellanby (1925) clearly showed that oatmeal and wheat possessed rachitogenic properties the significance of his findings was not generally appreciated. The later observations of other workers, including the senior author

of the present paper (McCance, 1934), suggested that phytic acid was the rachitogenic agent, but there was nevertheless a great reluctance in many quarters to accept the existence of a decalcifying factor in cereals. More recently Harrison & Mellanby (1939) showed that diets could be made rachitogenic for puppies by addition of sodium phytate and Mellanby (1941) has demonstrated that when oatmeal is boiled with HCl its rachitogenic properties disappear as its phytic acid is destroyed.

The present authors (see BMB **15**, below) found that men and women absorbed calcium and magnesium less freely when their diets contained much brown bread than they did when their diets contained the same amount of white bread. It was suspected that the substance responsible for the poor absorptions was phytic acid, which forms insoluble calcium and magnesium salts. Brown bread contains this substance, but white bread does not. These suspicions were confirmed when it was shown that if sodium phytate was added to white bread the absorption of calcium was inhibited.

In the present paper the authors describe the preparation of a brown flour containing no phytic acid and a study of its effect upon calcium absorption. The phytates were destroyed by enzymic hydrolysis, and the technical arrangements allowed the products of hydrolysis (inositol and inorganic phosphates) to be incorporated in the diet or excluded as desired. Control experiments were carried out on white and brown bread diets. There were 6 human subjects—3 men and 3 women. The results showed that calcium absorption was lowest when the diets contained untreated brown bread. Destroying the phytates improved the absorptions, and removal of the products of hydrolysis made a further improvement. With brown bread treated in this manner, calcium absorption was as good as with white bread. Similar results were obtained by the study of magnesium and phosphorus absorptions under similar conditions.

Taken in conjunction with previous findings, these results leave little room for doubt that phytic acid is the agent in whole wheat primarily responsible for the poor absorptions of calcium and magnesium, and they confirm that phosphorus in phytic acid is absorbed less readily than inorganic phosphorus.

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15

MINERAL METABOLISM OF HEALTHY ADULTS ON WHITE AND BROWN BREAD DIETARIES

by R. A. McCance and E. M. Widdowson, *Journal of Physiology*, **101**, 44–84, 2/6/42

The elaborate balance experiments described in this paper by two well-known British experts on Nutrition were carried out over a period of nine months on five healthy men and the same number of women. The work, which was supported by the Medical Research Council, was designed to show (*a*) whether calcium is absorbed less freely from brown than from white bread, and if so, (*b*) whether the phytic acid in whole cereal is responsible, (*c*) whether extra vitamin D increases the absorption and balance of calcium, (*d*) whether addition of calcium salts to wholemeal bread overcomes its bad effects on absorption, and if so which is the best salt and how much of it is required.

The absorption and excretion of calcium, magnesium, potassium and phosphorus were studied when 40–50% of the calories were provided by the following wheat flours—69% extraction (*i.e.* a flour representing 69% of the whole grain); 92% extraction; 69% and 92% extraction fortified with calcium carbonate or monohydrogen phosphate; 60% extraction with sodium phytate; 92% extraction and 2,000 international units of calciferol daily. The remainder of the diet consisted of the ordinary rations with restriction of milk and the exclusion of cheese; legumes were eaten sparingly and plants containing much oxalic acid were avoided.

It was found that Ca, Mg, P and K were less completely absorbed from the 92% flour than from that of 69% extraction. In defining calcium requirements it is therefore essential to state the nature of the cereal in the diet. Sodium phytate decreased the absorption of Ca and Mg but not of K. This showed the importance of phytic acid in cereals as a precipitating agent for Ca and Mg and indicates that the laxative effect of high extraction flour is not the major cause of the diminished absorption. About half of the phosphorus given as sodium phytate was absorbed. Extra vitamin D had no significant effect on the absorption of calcium in diets containing high extraction flour, but the addition of calcium salts to the flour increased the amount of calcium absorbed and converted a negative balance into a positive one. The carbonate and phosphate were equally effective and the carbonate is recommended as the phosphated white loaf is not so appetizing, whereas the carbonated loaf is, if anything, more so. As was expected the addition of calcium carbonate slightly depressed P absorption, but even with flour of low extraction the amount of P absorbed was sufficient for normal metabolism.

From careful analyses of the data it is recommended that flours used during the present emergency should have calcium carbonate added to them in the following amounts per 100 g. flour: (*a*) white flour, 65 mg.; (*b*) the British official 85% extraction flour, 120 mg.; (*c*) 92% extraction flour, 200 mg.

16

CIRCUMCORNEAL INJECTION AS A SIGN OF RIBOFLAVIN DEFICIENCY IN MAN—WITH AN ACCOUNT OF THREE CASES OF ARIBOFLAVINOSIS

by H. Scarborough, *British Medical Journal*, **2**, 601–604, 21/11/42

In 1938–39 Sebrell & Butler described a specific syndrome of riboflavin deficiency in man characterised by undue redness of the vermilion areas of the lips, by fissuring of the lips and by cheilosis. To these stigmata were added by other workers—dermatosis, glossitis, circumcorneal injection and keratitis. The ocular manifestations of ariboflavinosis were fully described by Sydenstricker, Sebrell, Cleckley & Kruse (1940), who considered the circumcorneal injection to be the earliest and commonest sign of the deficiency. It was often associated with subjective ocular sensations. These workers used the slit-lamp microscope to determine the presence and extent of the circumcorneal injection, and they were able to demonstrate actual invasion of the cornea by capillaries in the majority of cases.

The present author examined 204 consecutive cases in the medical out-patient department of the *Edinburgh Royal Infirmary* for the presence of circumcorneal injection. No slit microscope was used. In 34·3% of the whole group, whose ages ranged from 12 to 69, circumcorneal injection was present: among subjects over 49 (63 cases) it was present in 68%.

The striking character of these results required explanation, and accordingly 8 subjects with circumcorneal injection but without alimentary disorder or other stigmata of deficiency disease, were investigated in more detail. Treatment with riboflavin in some cases given both orally and parentally, and in a total dosage of 84–144 mg., failed to resolve the circumcorneal injection which also resisted treatment with brewer's yeast.

A second group of 8 subjects with circumcorneal injection but with stigmata of frank deficiency disease was also treated with large doses of riboflavin. Of these 5 were either cured or improved in respect of their circumcorneal injection.

There is therefore a form of circumcorneal injection, indistinguishable clinically from that due to riboflavin deficiency, which is not resolved by this vitamin. It may be present even in subjects with other vitamin deficiency diseases. These findings suggest that circumcorneal injection can be considered as evidence of riboflavin deficiency only in the presence of collateral evidence of deficiency of this vitamin (cheilosis, glossitis, dermatosis and ocular symptoms), or as a result of slit-lamp examination of the edge of the cornea, or, best of all, as a result of a therapeutic test.

The author describes three cases of ariboflavinosis in detail. In all cases the rapid relapse when treatment was

discontinued was very striking. It is therefore suggested that certain individuals, for reasons at present unknown, manifest a requirement for riboflavin which is abnormally great.

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17

THE EFFECT OF ASCORBIC ACID (VITAMIN C), CALCIUM ASCORBATE, AND CALCIUM GLUCONATE ON THE REGENERATION OF BONE IN RATS

by G. Bourne, *Quarterly Journal of Experimental Physiology*, **31**, 319–331, July, 1942

There is abundant recorded evidence that ascorbic acid is associated with the formation of collagen fibres, and it has also been shown that there is imperfect regeneration of bone in scorbutic animals. The present author has conducted experiments designed to determine whether the administration of ascorbic acid in quantities in excess of those needed to saturate the organism with the vitamin can produce an acceleration of the rate of regeneration of bone.

Comparative estimates of the rate of regeneration of bone in rats was obtained as follows. Small holes of a standard size (1 mm.) were bored in the femurs of the rats and the volumes of the trabeculæ which formed in such holes at the end of a week were measured.

Five groups of rats were used and the following substances were injected subcutaneously each day.

1. Normal saline, 1 cm^3.
2. Calcium ascorbate, 50 mg. (equal to 5 mg. of calcium and 45 mg. of ascorbic acid).
3. Calcium gluconate (an amount equal to 5 mg. of calcium).
4. Ascorbic acid, 45 mg.
5. Ascorbic acid, 45 mg. and calcium gluconate (an amount equal to 5 mg. of Ca).

At the end of one week it was found that the volume of trabeculæ formed in group 2 (calcium ascorbate group) was greater than that formed in any other group, and that the difference was statistically significant. None of the other groups differed significantly from group 1 (the controls) in respect of the amount of trabeculæ formed. The smallest amount of trabeculæ was formed in group 5.

Calcium ascorbate supplies calcium and ascorbic acid together, and both these substances are essential for the healing of bone. The results of this investigation suggest that calcium ascorbate may prove useful in accelerating the rate of healing of fractures in human beings.

18

VITAMIN C AND REPAIR OF INJURED TISSUES

by G. H. Bourne, *Lancet*, **2**, 661, 5/12/42

In this paper from the *University Laboratory of Physiology*, Oxford, the author draws attention to the accumulation of evidence of the importance of ascorbic acid in the regeneration of tissues. The older medical literature contains many references to the failure of wounds to heal in scurvy and of the tendency for old wounds to break open again. The publications of Aschoff and Koch on the microscopical pathology of human scurvy in 1919 and Höjer's work on experimental scurvy in guinea pigs established that there was widespread degeneration of bodily tissues as a result of this disease.

Many workers (Höjer, 1923; Wolbach & Howe, 1925; Jeney & Törö, 1936; Mazoué, 1937; Quérido & Gaillard, 1939; and Hunt, 1941) have established that ascorbic acid is essential for the production and maturation of collagen fibres in the body tissues. Ishido (1923), Saitta (1929), Lauber (1933), Bourne (1942), and others showed that, in animals with diets deficient in this vitamin, wounds had a much lower tensile strength than normal. Bartlett, Jones & Ryan (1942) found that the scar tissue of animals on low ascorbic acid intakes contained less of the vitamin than the scar tissue of normal animals. As a result of these findings many writers now stress the importance of adequate amounts of ascorbic acid for surgical patients.

As ascorbic acid plays an important part in the production of tissue fibres it is obvious that it must play an important part in the healing of bone. In a scorbutic animal there is no inflammatory reaction to bone injury and therefore normal healing processes cannot be initiated. The present author (Bourne, 1942) found that the amount of bone regenerated by an injured area of femur of a guinea pig was directly dependent upon the amount of ascorbic acid given to it, reaching its optimum amount at a level of 2 mg. of the vitamin per day. Giangrasso (1939) was able to secure more rapid healing of fractures in rabbits by administering ascorbic acid, which rabbits are supposed to synthesise, but the present author (Bourne, 1942) was unable to obtain the same result with rats (which also synthesise it).

Although it is established that ascorbic acid is essential for the production of the organic foundation material of bone it is not generally realised that it is also essential for calcification. In scurvy, calcium ceases to be deposited on bones and it has been shown by Gould & Schwachman (1942) and by the present author (Bourne, 1942) that in scorbutic animals the phosphatase activity of bones is reduced. Ruskin (1938) believes that ascorbic acid forms on absorption with calcium a Ca–ascorbic-acid–protein complex.

From the results presented in this paper it appears that ascorbic acid plays a fundamental part in the regeneration of tissues and for this reason it seems that the administration of the vitamin should become a routine in the treatment of any injury. Preliminary results with animals (see BMB 17, above) suggest that calcium ascorbate may be a valuable therapeutic substance for the treatment of fractures, but clinical trials with this compound have not yet been carried out.

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19

AORTIC SIZE, STATUS LYMPHATICUS AND ACCIDENTAL DEATH

by W. G. Millar and T. F. Ross, *Journal of Pathology and Bacteriology*, **54**, 455–460, October, 1942

The ill-defined condition of "status lymphaticus" has for long been believed to be associated with sudden unexpected death from relatively trivial accidents, anæsthesia, and other factors not normally regarded as sufficient single causes of death.

Enlargement or persistence of the thymus, generalised enlargement of lymphoid tissue, and a small calibre of the aorta have been alleged to be the main characteristics of the condition, although thymic enlargement as a criterion was discredited by the investigations of the *Status Lymphaticus Committee* of the Pathological Society of Great Britain and Ireland (Young & Turnbull, 1931). In the experience of the present authors, the alleged characteristics of the condition vary considerably, but the most constant is narrowness of the aorta. As this is also the most easily measured characteristic, the present investigation was undertaken on the aortas

of a series of cases coming to autopsy at the *Edinburgh Royal Infirmary* with the object of ascertaining whether a relationship exists between death from accident and poor vascular development.

The mid-thoracic circumference of 300 aortas was measured to the nearest millimetre. Vessels showing gross degeneration and those from hypertensive, emaciated, obese, or œdematous subjects were not measured. The values were corrected by the method of multiple regression for variations dependent on age, height, weight, and sex. Those from 26 accident cases had a mean circumference of 51·05 ± 0·49 mm., while those from 274 cases dying of natural causes had a mean circumference of 52·53 ± 0·25 mm., a difference of 1·48 ± 0·55 mm. This difference is statistically significant (P = 0·0076). By using ungrouped figures and including "accident versus non-accident" as a fifth independent variable in the multiple regression equations, the difference rises to 2·56 ± 0·83 mm. (P = 0·003). The variance of the accident values is also significantly lower than that of the non-accident cases.

The authors regard the results as indicating a real (and probably congenital) difference, as all obvious causes of dilatation of the non-accident aortas appear to be allowed for and as those accident aortas which are obviously narrow are also thin-walled. This hypoplasia of the aorta is regarded as being similar to or identical with that described in *status lymphaticus*, which is thus thought to be a real entity. The authors find it difficult to believe that the connection between aortic narrowness and liability to sudden death is a direct one. They suggest instead that subjects with this defect may be specially liable to or less able to avoid accidents, and that for this reason they tend to appear on the post-mortem table.

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20

THE PRESERVATION OF Vi ANTIGEN IN T.A.B.C. VACCINE: WITH A NOTE ON COMBINED ACTIVE IMMUNIZATION WITH T.A.B.C. VACCINE IN TETANUS FORMOL-TOXOID

by S. G. Rainsford, *Journal of Hygiene*, **42**, 297–322, May, 1942

It is essential that T.A.B.C. vaccines for use in the Navy should, in addition to possessing unaltered O and Vi antigens, be able to retain these antigens in active form when stored for many months at 23°–25° C. The antigens are fully retained in vaccines sterilized by merthiolate, colloidal silver, alcohol or acetone, but, while these agents may be successfully used as preservatives when the vaccine is stored in the ice-box, the Vi antigen, as detected by its power to stimulate Vi antibodies in the rabbit, is seriously impaired in a few months at 23°–25° C.

The author's experiments were directed to finding a means of increasing the heat stability of the Vi antigen and in this he was assisted by the observation that exposure to short periods at 37° C. or 60° C. has the same effect as exposure to long periods at 23° C. The key to the problem appeared to be dehydration of the bacilli, and vaccines desiccated by acetone or suspended in 32% saline were found to retain Vi antigen for a year at 23°–25° C. The protocols show that a vaccine sterilized by 1/2000 merthiolate in 32% saline and preserved with 1/10,000 merthiolate in 32% saline still stimulated in rabbits a high titre of O and Vi antibodies after 21–50 days at 37° C. and after at least 6–7 months (the longest time yet available) at 23°–25° C., and that the antibodies were fully potent in the mouse-protection test.

In view of recent work (Felix, 1941; Felix, Rainsford & Stokes, 1941) on T.A.B. vaccines sterilized and preserved with alcohol, it may be noted that the present author reports that a vaccine killed by 75% alcohol in physiological saline, washed and resuspended in 25% alcohol in saline, retained little or no Vi-stimulating capacity after 21–30 days at 37° C. No information is available regarding the behaviour of this vaccine at lower temperatures.

Full details are given of the preparation of (1) dried T.A.B.C. vaccine, to which the necessary volume of merthiolate in saline, issued separately in a vaccine bottle, is added by syringe just before use, and (2) T.A.B.C. vaccine using 32% saline with merthiolate. The latter is easier and cheaper to prepare and is to be preferred for routine work.

The effect of mixing T.A.B. vaccine with tetanus formol-toxoid was also examined. The results suggest that this procedure, owing to the formol or to the phenol used to preserve the toxoid, results in a marked decrease in the immunogenic properties of the Vi antigen. The phenol cannot be replaced by merthiolate as the bacteriostatic properties of the latter are destroyed by sulphur derivatives (sodium metabisulphite is used to neutralize the free formalin after toxoiding). The addition of tetanus formol-toxoid to dried vaccine just before administration did not solve the problem, which must await further enquiry.

The author points out that the older vaccines, though inferior to the newer types in experimental immunization against typhoid, are nevertheless known to have been valuable in practice, perhaps owing to their ability to sensitize the tissues to Vi antigen, and that it is not known how admixture with formol-toxoid affects this property.

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21

ABSORPTION OF SULPHANILAMIDE APPLIED LOCALLY: BLOOD LEVEL IN 41 CASES

by A. R. Hodgson and J. R. Robinson, *Lancet*, **2**, 392–394, 3/10/42

The sulphonamides are now widely used by local application in the treatment of traumatic and surgical wounds. The authors have observed that this treatment may give rise to toxic manifestations in the first few days of the post-operative period, including anorexia, nausea, vomiting, cyanosis, depression and prostration. The occurrence of these symptoms indicates that the rate of absorption of the drug into the blood-stream must be high.

The present paper reports an investigation to determine the blood concentrations attained after the local application of sulphanilamide. A measured amount of the powder, usually 15 to 20 grams, was introduced into the wound after excision of skin edges and devitalised tissue. Estimations of the blood concentration of sulphanilamide were made by the method of Werner (1939). Only free sulphanilamide was estimated and errors were probably of the order of plus or minus 5%.

Venous blood was taken at 6-hourly intervals, and the peak concentration in 41 subjects was usually at about 24 hours. The degree of absorption was expressed as the blood concentration in mg. per 100 cm^3. attained per gram of sulphanilamide inserted. In over 90% of cases a figure of 0·8–1·2 was obtained. Absorption was least from wounds of the hands and feet and greatest from wounds of the trunk.

Referring to the effect of local application of sulphanilamide on wound healing and infection, the authors state that there was no trace of the drug in wounds re-opened 4–10 days after the first operation. Healing of the wounds appeared to be slightly retarded. In no case was a clean operation wound found to be infected when exposed for removal of sutures.

The conclusions drawn from this investigation are that (1) a blood concentration of approximately 1 mg. free sulphanilamide per 100 cm^3. is obtained for each gram of sulphanilamide locally applied, (2) simultaneous oral administration of sulphonamides is unnecessary in many cases, (3) care should be taken to avoid applying locally a sufficient quantity of sulphanilamide to produce toxic manifestations by absorption into the blood-stream.

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22

ENTERITIS IN A NURSERY HOME ASSOCIATED WITH GIARDIA LAMBLIA

by G. Ormiston, J. Taylor and G. S. Wilson, *British Medical Journal*, **2**, 151–154, 8/8/42

This paper is based on a report to the Medical Research Council from an *Emergency Public Health Laboratory* (one of a number of similar laboratories which have been organised by the Council to provide an efficient national bacteriological

service). The report is of special interest because little attention has been paid in recent years to *Giardia lamblia* (*G. intestinalis*) infections and because there is reason to suspect that the condition is commoner than has been generally supposed.

The outbreak of enteritis described, much of it of a chronic type, affected a high proportion both of children and adults in a residential nursery for evacuees. *Giardia lamblia* was found in 71% of children and adults having loose stools at the time of examination, and in only 32% of those with normal stools. The protozoon was also found in 82% of children and adults with a history of intermittent or continual loose stools for some months, and in only 25% of those without such a history.

Cure of the infection was quickly and successfully accomplished by the oral administration of mepacrine hydrochloride (Atebrin, Quinacrine). Children received 16 mg. and adults 100 mg. three times daily for 5 days.

The symptoms—chronic diarrhœa and some degree of anæmia in the children, and diarrhœa with giddiness, loss of energy, anorexia, headache, and epigastric discomfort in the adults—disappeared after treatment, the general nutrition of the children improved, and the stools were free from *Giardia*. The course of treatment was repeated after a 3-day interval.

The high frequency of *Giardia* in the stools of the patients with long-standing diarrhœa and the favourable effect of treatment suggest that this organism was probably responsible for the chronic enteritis observed in this nursery. Further observations, however, are necessary to establish the exact degree of pathogenicity of *Giardia* for man.

23

POSTVACCINAL ERUPTIONS

by E. Bloch, *Lancet*, 2, 504–507, 31/10/42

The author, who is Divisional Medical Officer to the *Glasgow Public Health Department*, records the recent entry of a previously unrecognised case of oriental smallpox in Glasgow. Within two months 34 further cases developed, with eight deaths. One month after the date of importation of the first case 25 public vaccination stations were opened. About half a million vaccinations were performed in the course of the next month. Many regional or generalised eruptions followed positive vaccination, but only a minority of these were reported to the medical officer of health.

The records of these reported eruptions are analysed. The clinical appearances were as follows: papules or maculo-papules 7, papular urticaria (lichen urticatus) 37, urticaria 6, erythema 29, erythema multiforme 26, petechiæ 2, pustular eruptions 15. Of these 122 cases, only 22 had been positively vaccinated in previous years. Ages at vaccination ranged from 6 weeks to 50 years. Seventy-five per cent. were under 15 years of age. Seventy-nine cases were females.

The interval between vaccination and eruption ranged from 2 to 27 days, but in the great majority was 7–11 days. Ætiological inquiries (lymph, vaccination-technique, home cleanliness, previous skin-disease, familial tendency) yielded negative results. The cases of lichen urticatus caused much difficulty in diagnosis but pruritus helped to exclude variola. The pustular group were chiefly cases of bullous impetigo. These simulated multiple auto-inoculations. No eruption was regarded as generalised vaccinia. One of the cases classed as pustular, a previously healthy infant aged 8 weeks at vaccination, died 10 days later of exfoliative dermatitis which was associated with impetigo. This was the only fatal case of postvaccinal eruption.

A small group of late or sequelar rashes appearing 7–11 weeks after vaccination was also reported. These were: a papular eczema of the vaccinated arm and of the adjacent part of the trunk, a generalised bullous impetigo with crusting of the vaccination, a first attack of papular urticaria, and 2 cases of erythema multiforme marginatum.

24

CEREBROSPINAL FEVER: A REVIEW OF 500 CASES TREATED BY CHEMOTHERAPY WITHOUT INTRATHECAL SERUM

by G.E. Harries, *British Medical Journal*, 2, 423–424, 10/10/42

The author of this paper is Lecturer in Infectious Diseases at the *Welsh National School of Medicine*. From January, 1940, to February, 1942, 500 consecutive cases of cerebrospinal fever admitted to the Cardiff City Isolation Hospital were treated by chemotherapy without intrathecal antimeningococcal serum. The youngest case was an infant of six weeks, who made a complete recovery. The oldest was a fatal case aged seventy years. All cases of cerebrospinal fever admitted during that period were included, even those which were moribund at the time of admission.

The gross mortality rate for the whole series was 8·6%. Excluding those that ended fatally within 24 hours of admission, the case mortality rate would be recorded as 4·8%. The most favourable age group (179 cases) was 10 to 30 years. In this group there was a case mortality rate of only 2·2%. Forty-four military patients in this series all recovered, probably because of their general fitness, favourable age grouping and early admission to hospital.

The author proposes a clinical classification of cerebrospinal fever which includes all types.

1. *Meningococcal septicæmic* type:
   (*a*) Waterhouse-Friderichsen Syndrome (with adrenal hæmorrhages, purpuric eruptions, pallor, and collapse).
   (*b*) Chronic meningococcæmia (with intermittent periods of pyrexia, usually petechiæ and arthritis, occasionally lesions resembling erythema nodosum, and rarely maculo-papular eruptions).
2. *Meningitic* type:
   (*a*) Acute.
   (*b*) Sub-acute.
   (*c*) Chronic (including the post-basic variety of Gee and Barlow in infants).
3. *Encephalitic* type with lesions deep in the nervous tissue. This type is very rare and highly fatal from frequent involvement of the brain stem.

Purpuric eruptions, generally petechiæ, which appeared on the first and second day of disease, were present in 55% of the patients in this series, and these were usually the most severe cases. Herpes was found in 49% of cases, usually towards the end of the first week of the disease.

The main complications were: transient strabismus, 77; broncho-pneumonia, 12 (usually confirmed *post mortem*); arthritis, 29 (mainly the larger joints); deafness, temporary and partial, 11, total and permanent, 7; transient albuminuria, 91; conjunctivitis or iridocyclitis, 17; transient paresis of arms, 3; temporary facial paralysis, 10; transient ptosis, 8; transient hemiplegia, 1; temporary mental derangement, persisting well into convalescence, 4; hydrocephalus, 5; dysphagia, due to severe neck retraction, 2; transient nystagmus, 2; orchitis, 1.

Treatment

Sulphapyridine was employed in 471 and sulphathiazole in 29 cases. Sulphathiazole was equally effective in promoting recovery but caused less nausea and vomiting than sulphapyridine. Both drugs were given in the following dosage: 2 grams by mouth on admission, repeated in 4 hours; then one gram 4-hourly for the next 72 hours. Then 0·5 gram 6-hourly for a further 3 days. After the first 250 cases the dosage was increased to 2 grams, 4-hourly for 4 doses and then 1 gram 4-hourly for 96 hours, followed by 0·5 gram 6-hourly for a further 3 days. The increased dosage was found to have a slight effect in diminishing recurrences and septic complications such as arthritis. Children under 12 years received half, and infants under 12 months a quarter of the adult dosage.

The average number of lumbar punctures performed per patient was 4. In all, 6 ventricular and 5 cisternal punctures were performed. If the patient was comatose, tablets were crushed and given by nasal feeds. If vomiting occurred after injections of the drug or if the patient was delirious and nasal feeding difficult, the sulphapyridine-sodium solution was injected intravenously with three times its volume of normal saline. In severe cases, or if there was much dehydration, sulphapyridine-sodium was given intravenously by the drip method in a litre of normal saline with 5% glucose. Fluids were given freely in all cases as dehydration contributes materially to a fatal issue. Also adequate fluids lessen the incidence of hæmaturia due to deposition of acetyl sulphonamide derivatives in the kidneys.

As extensive hæmorrhages are often found in the adrenals in acute septicæmic cases 5% glucose saline (1 litre) was given

intravenously as indicated above, as sodium chloride and glucose are advocated in cases of adrenal damage. Such cases also received desoxycorticosterone acetate intramuscularly and, to combat toxæmia, 30 to 60 cm³. of meningococcal anti-toxin was also given intravenously in the glucose saline. Several patients whose pulses were imperceptible recovered when thus treated.

No person in attendance contracted the disease, though no masks were worn. The giving of small prophylactic doses of sulphonamides in suspected cases was without effect on the meningococci except that the organism appeared to be rendered drug-resistant and large doses administered later seemed less effective. Two patients who had neck retraction of such a degree as to prevent deglutition were successfully treated by the injection of a few cm³. of procaine solution into the post-cervical muscles.

Morphological meningococci were found in the cerebrospinal fluid in 93% of cases. Cultures were obtained in 214 cases—93% belonging to Group I and 3·7% to Group II, while 3·3% were inagglutinable.

Clinically the various strains seemed to be of equal virulence.

25

DIPHTHERIA : SOME RECENT OBSERVATIONS ON SUSCEPTIBILITY

by J. Grant, *Medical Officer*, 68, 149–151, 7/11/42

After some years of low prevalence, diphtheria became epidemic in the Tyneside town of Gateshead in 1936. Up to the end of 1941, 1,743 verified cases had been admitted to hospital and these included a large proportion of the hypertoxic clinical type of the disease. *Gravis* strains were frequent among the causal bacilli and later predominated. In 1941, especially in the autumn, the disease was particularly aggressive and infectious, and a number of anomalous experiences were noted in that year. These were the occurrence of diphtheria in inoculated children, in Schick-negative nurses of the hospital staff, and in patients who had already suffered a previous attack.

Immunisation of children against diphtheria was begun late in 1940 and is continuing. At the end of 1941, 4,671 children had been completely inoculated out of a child population of 24,258. The first 630 of these had a single large dose (0·5 cm³.) of alum-precipitated toxoid (APT) and the remainder either 2 doses of this product (0·1 cm³. and usually 0·5 cm³.) or 3 doses each of 1·0 cm³. toxoid-antitoxin floccules (TAF).

In 345 verified cases of diphtheria admitted to hospital in 1941, there were 13 fully inoculated patients, of whom 4 were children previously inoculated with the single large dose of APT, 8 were children who had received the two doses of APT, whilst one was a nurse who had received 3 doses of TAF and was subsequently Schick-negative. One of these children died, and in 5 others the disease was severe. Two of the children had also had previous attacks of diphtheria, while two others, including the fatal case, suffered the infection two months after completion of the inoculation. Incidence rates of the disease during the last three months of 1941 were 2·44 per 1000 for inoculated children and 6·07 in non-immunised children.

Seven nurses belonging to the isolation hospital staff suffered the disease although they had previously been found Schick-negative. None of the attacks was severe.

The author gives details of 13 alleged second attacks of diphtheria in 1941. Two of these cases are not accepted as diphtheritic, leaving 6 certain and 5 probable second attacks. Of the 6 certain attacks, one was severe, 3 moderate and 1 mild. In 1941, the incidence of proven diphtheria in children who had already survived an attack of diphtheria was at the rate of 4·38 per 1000 in contrast to that of 11·5 per 1000 of the general child population. In Gateshead the practice is to search for contact " carriers " among the domestic child contacts of cases of diphtheria. Comparison of carrier incidence among these showed that 303 non-inoculated contacts yielded 51 carriers (17%), while 70 inoculated contacts yielded 7 carriers (10%).

In conclusion, the author suggests the possibility that certain individuals cannot be immunised for a lasting period because of an innate deficiency, and that the *gravis* strains of diphtheria bacilli may be capable of overcoming an immunity which would be sufficient protection against diphtheria due to other strains. He argues that community immunisation should not result in an increase of the number of diphtheria carriers.

In a postscript relating to the first half of 1942, the author shows that similar experiences continue. It has since been shown that one of the preparations of APT used was defective. This prophylactic had been used in some, but not all of the inoculated patients who contracted diphtheria, and the author claims that his main conclusions are not affected.

26

THE CANCER ACT

by R. Paterson, *Lancet*, 2, 317–320, 12/9/42

This paper by the Director of the Radium Institute, Manchester, is a well-informed survey of possible developments which may arise from the British Cancer Act of 1939. Under this Act every local authority becomes responsible for the care of patients with cancer, and will have to provide facilities for diagnosis, expert radiological and surgical treatment, an effective system of recording the history of every case and following its progress throughout, and suitable popular education or propaganda measures.

The author, basing his calculation on the Registrar General's reports, estimates that in a population of one million, 2,000 new cases of cancer, excluding rodent ulcer, may be expected during each year, and that 900 of them will require treatment in special centres. He believes that hopeless cases would be best treated at home and he suggests that an addition might be made to the Cancer Act providing for the home-nursing of these patients.

There will be general agreement with the author when he says that, whatever arrangements may be made, two general principles must be accepted. The first is that as soon as cancer is suspected, action must follow immediately, and the second is that all specialists concerned with diagnosis and treatment must be engaged in cancer work to such an extent that they really have special experience of this group of diseases.

The author believes that propaganda should be confined to the four curable types of cancer, namely, those affecting the breast, mouth, skin and uterus. He points out that in no other forms of malignant disease will education or propaganda have any great influence. Other matters of interest are raised in this thoughtful review, and those with a special interest in the cancer problem should refer to the original paper.

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SPECIAL CONTRIBUTION

MEDICAL EDUCATION IN GREAT BRITAIN

by H. P. HIMSWORTH, M.D., F.R.C.P.

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To understand any existing scheme of organisation it is first necessary to examine its antecedents. This is no less true of systems of education. Broadly speaking, the different systems of medical education which exist to-day had their origin from one of two distinct sources. They either arose from university departments of theoretical medicine or they arose from a system of apprenticeship to practising doctors. Medical education in England sprang from the latter source, and to-day the traditions of apprenticeship, though now developed and modified, are still responsible for its most characteristic features.

In the mediæval University, teaching was characterised by authoritative statement and little more was expected from the student than that he should imbibe without question the information thus presented. Under such a system the role of the student was largely passive, personal contact between teacher and learner was not fostered and the road to success lay in unquestioning acceptance of authorised beliefs rather than in personal observation of actual sick patients. The method of the apprentice system was entirely different. Its keynote was personal experience, and to this end the student attached himself to a master of the craft whom he assisted in the actual practice of his art. An intimate contact between teacher and student thus arose; a contact in which the teacher felt a personal responsibility for the education of his student and in which the student was able to discuss his difficulties, report his observations and judge his teacher by the test of actual competence. The different influences of these two systems still mould modern medical education. In those countries in which the teaching tradition springs from the mediæval University, the centre of the teaching is the formal lecture or lecture-demonstration; in those countries such as England, in which teaching derives from the apprentice system, the centre of the teaching is the actual care of patients by the students acting under the personal supervision of the teacher.

With the advancement of medical knowledge, however, the original primitive apprenticeship proved inadequate as the sole basis of training, and rapidly, perhaps because of the relative freedom of this system from authoritative doctrine, new methods of training were incorporated. Anatomy was early taught systematically, morbid anatomy soon followed, and then there was a pause until the great schools of physiology and pathology arose and in their turn were taken into the system.

These are the forces which have shaped, and are still shaping, British medical training, and it is now proposed to outline the actual scheme which they have brought into existence.

The course of medical training lasts 5½ to 6 years and the student usually commences the course at the University when he is 18 or 19 years of age. Before entering the University he must have taken an examination in general education, languages, mathematics, and at least one, more usually two, branches of science. The first year is spent in a further study of chemistry, physics and biology and at the end of this time he takes his first medical examination. After passing this examination he studies anatomy, physiology, biochemistry and pharmacology for a period of eighteen months and then takes his second medical examination.

Superficially this scheme of education differs little from that existing all over the world; but in practice there are certain significant differences. For example, relatively few lectures are given in the anatomy course; instruction is gained almost entirely from dissection. Each student dissects the whole body. On his own responsibility he dissects a particular region and then a demonstrator questions him on his findings and explains difficulties. Again in the physiology course, although there are many lectures, all students carry out numerous experiments for themselves. Of recent years these two courses have become increasingly directed to the living subject. Much anatomy is learnt now by the students on their own bodies and the functional aspect of the structures studied is stressed. In physiology most experiments are on the human subject; reflex action, metabolism, etc. are investigated by the students on their own persons. But perhaps the most obvious influence of the apprentice tradition is seen in all these subjects in the striving, whenever possible, to avoid large classes and to give individual and personal tuition to small groups of students.

After passing the second medical examination, the student enters the hospital. Here he is exposed to the two different methods of teaching. In pathology, bacteriology, etc., the teaching is predominantly academic in type, although the same tendencies as were noted in the teaching of physiology and anatomy ensure that individual tuition and the performance of experiments by the student play a prominent part in the course. It is in the teaching of the actual clinical subjects that the characteristics of British medical education are best seen. After a preliminary course of three months, in which the student learns under supervision how to question and examine the patient and to carry out simple investigations on the blood and urine, the students are divided into small groups, each of six or eight persons, which are known as "firms." Each firm is accredited to a member of the hospital staff who has an intern and a registrar (junior physician or surgeon) to assist him. The student now finds himself responsible for certain aspects of the care of four or five patients. He must question the patient and write an account of the illness; he must examine the patient and record his findings; and he carries out the simpler chemical investigations required. In case of difficulty he may ask help of the registrar who, in any case, checks the student's notes and points out any errors. The physician or surgeon in charge of the firm visits the patients with the students and on such visits each student is questioned, and asks questions, about the patients for which he is responsible. Each firm is also responsible for an out-patient clinic, and here also the student takes an active responsibility in dealing with the patients. In addition to such visits with his own firm the teacher takes larger groups of students round the wards. On these occasions it is the custom to select cases of a similar type or dissimilar patients illustrating a particular important clinical point and, starting with the actual patients present, to discuss the whole problem of which they constitute examples.

The first firm to which the student is attached is usually a medical firm. Thereafter he is appointed to a surgical firm, an obstetric firm, an ophthalmological firm, the clinical pathology unit and so on. On the surgical firm he not only carries out the duties mentioned above but he assists with operations, dresses the wounds after operation, and in the out-patient clinic takes part in the treatment of minor injuries and surgical conditions. During his appointment to the obstetric firm he delivers women both in hospital and in their own homes.

It should be clearly understood that it is compulsory for all students to serve appointments in all branches of clinical medicine. A student might wish to take some appointments and not others; he must, however, take all, and before he can enter for his final qualifying examination he must produce a certificate showing that he has discharged his duties satisfactorily in every one of his clinical appointments.

It will thus be seen that the keynote of clinical teaching in Great Britain is to give the student personal contact with sick persons. As, however, in the short period of medical training a comprehensive experience is unlikely to be gained through personal experience, this teaching is supplemented

by lectures and lecture-demonstrations. It is significant, however, of the relative importance attached to clinical instruction on actual patients and to teaching by lectures and demonstrations that, whilst the former is compulsory, attendance at all lectures is generally optional.

An innovation in practical teaching which is meeting with much success is the clinico-pathological meeting. For some years now such meetings have been held between the members of the clinical staff of the hospital and the pathologist, and the full and frank discussions on fatal cases thus made possible have undoubtedly been of great value. At some hospitals such meetings are now being held with students and they are proving such a success that they are likely to be generally adopted. At these meetings the student who has attended the patient during life first gives an account of the case, and the pathologist then discusses the *postmortem* examination. The students then discuss the case and question, and not infrequently criticise, the physician or surgeon who was in charge of the patient. Finally, the physician or surgeon discusses the case as a whole and the condition of which the case is an example,

It will be appreciated that under the system described considerable freedom is given to the individual teachers and the different medical schools to develop their courses of instruction according to their particular ideas on the subject rather than in conformity to a rigid schedule of academic instruction. This liberty is further facilitated by the fact that there is no State qualifying examination in Great Britain. The final examination of each University and of each of the independent Colleges of Physicians and Surgeons qualifies the holder to be entered in the official register of medical practitioners and thus to enjoy the legal privileges and responsibilities of a recognised practitioner of medicine.

It might well be asked whether the system taken as a whole does not allow too much liberty so that there is a real danger that the many different examinations may differ widely in standard. If there were no further safeguard this possibility would undoubtedly exist; but the danger has been foreseen and provided against. A body called the General Medical Council has long been in existence. This body, set up by the authority of the Government, is composed of medical men, and one of its duties is to lay down the general scheme of medical teaching and the minimum standards which a final examination must attain if it is to be accepted as entitling the holder to registration as a practitioner. This Council has considerable power, for it can, if it considers fit, refuse to recognise a particular final examination as entitling to registration. In practice the Council has used its powers wisely. Instead of laying down rigid and detailed schedules of clinical instruction, which it might well have done, it has contented itself with indicating on very broad lines the scope of medical teaching considered desirable. In this way it has left the different Universities and Colleges the freedom within wide limits to follow their own inspiration regarding teaching. Similarly the Council has not constituted itself an examining body. It has allowed the different teaching bodies to conduct their own examinations but, at the same time, it has controlled the general standard of the qualifying examination by appointing inspectors to attend, to report on and, should they so desire, to take part in these examinations.

In this brief outline of the British system of medical education as it exists to-day, an attempt has been made to display the principles which inspire the methods used. The system is now very different from the simple apprentice system from which it derived, but it still retains certain characteristics of that system. Not least of these is an ability rapidly to adjust practice to experience even in the matter of education; and in this it would seem to have an advantage over more rigid and doctrinaire systems.

Dr. Himsworth was appointed Professor of Medicine at University College Hospital, London, in 1939. He has been responsible for researches into the nature of metabolic diseases, especially diabetes mellitus, the functions of the endocrine glands concerned with metabolism, and the pathogenesis of necrotic and cirrhotic conditions. Since the war he has been honorary secretary of the Medical Research Council's Committee which advises on the distribution of food to invalids and persons on special diets. He is also a member of the British Medical Association's Commission for the replanning of the British medical services and of a committee of the Royal College of Physicians on the replanning of Medical Education.

28

PARATYPHOID FEVER: AN EPIDEMIOLOGICAL STUDY

by W. Savage, *Journal of Hygiene*, 42, 393–410, July, 1942

The author, who is a British public health administrator of long experience, especially in the bacteriology and epidemiology of infections conveyed by foodstuffs, has made a valuable survey of outbreaks of paratyphoid B fever. He has taken as his material the data from forty epidemics which occurred in Great Britain between 1923 and 1941, supplemented by observations from certain American outbreaks. One object of the study was to compare the characters of paratyphoid fever with those of typhoid fever and food-poisoning due to organisms of the Salmonella group.

While paratyphoid B fever usually takes the form of a prolonged febrile illness of "enteric" type, cases may start with vomiting and diarrhœa, and thus resemble acute food-poisoning. In one outbreak where there was a massive infection, 43 out of 56 persons affected had these initial symptoms, and in 9 of them the usual enteric type of illness did not develop.

The incubation period, which is usually about 10 to 12 days, may be as long as 24 days or, if the infecting dose is large, as short as 4 days. The vehicle of infection will largely determine the age and sex distribution of the cases. For example, the majority of patients will be children when the infection is conveyed by ice-cream. In Great Britain epidemics have usually commenced in early summer.

Waterborne outbreaks are rare and in the authenticated instances pollution of the supply has been very heavy. In 80% of the epidemics some article of food was responsible, and in 40% that article was cream, especially artificial cream used for cake fillings.

The responsible food is usually one in which the organism can multiply, and when the food has been kept for a time in warm weather a high proportion of those consuming it may become infected. Except in these circumstances, however, the proportion of those at risk who develop the disease may be small, and outbreaks may show an intermittent rather than an explosive character.

Almost invariably numbers of persons will be found to be excreting the organism without symptoms. These individuals, unrecognised ambulant cases and convalescent patients continuing to excrete *Bact. paratyphosum B*, are the persons likely to start or spread an outbreak. Careful study of the history and of the bacteriological and serological findings may be necessary to determine whether such a person is the cause or a victim of a particular epidemic. In the present series chronic carriers could rarely be proved responsible.

In its case-mortality (at most 1·76% for this whole series) and the necessity for a large infecting dose, paratyphoid B resembles Salmonella food-poisoning. In contrast to the typhoid bacillus which is invasive and strictly parasitic on man, the Salmonellas are irritant, non-invasive and parasitic on many animal species. The author's view is that *Bact. paratyphosum B* is in the process of evolution from a Salmonella-like ancestral type towards an invasive typhoid-like type of organism. With the possible exception of several reported outbreaks associated with dogs in Scandinavia, *Bact. paratyphosum B* is parasitic only to man. Strict parasitism to a single host cannot readily be maintained by an organism with irritant properties as these lead to rapid expulsion from the body. Invasive properties, associated with bacteræmia and growth in the body tissues, are therefore being evolved. The symptoms and epidemiology of paratyphoid B lend considerable support to this theory.

29

IMMUNISATION WITH T.A.B. IN AN OUTBREAK OF PARATYPHOID FEVER

by E. C. Dax and D. M. Stone, *Lancet*, **2**, 422–424, 10/10/42

A Medical Superintendent of a mental hospital and a Bacteriologist to an *Emergency Public Health Laboratory* report an outbreak of paratyphoid fever among a mixed group of demented and mentally defective patients. In the hospital involved, only one villa, which accommodated 80 patients, was affected. The majority of these were incontinent and unclean in their habits, and 19 of them developed symptoms of pyrexia with acute gastro-enteritis. There were 4 deaths, all in idiots.

Nineteen days after the first case occurred, those patients who had shown no clinical signs of the disease were given, at weekly intervals, 3 doses (0·2 cm.^{3}, 0·5 cm.^{3} and 1 cm.^{3}) of a T.A.B. vaccine containing 1000 million *Bact. typhosum*, 700 million *Bact. paratyphosum A* and 500 million *Bact. paratyphosum B* per cm.^{3} The epidemic ceased abruptly after the first dose of vaccine, although previously cases were becoming more frequent. Twenty-three additional patients were then found to be excreting *Bact. paratyphosum B* in their fæces without showing any clinical evidence of infection.

Fæces were examined by culture on McConkey's medium (a) directly and (b) after preliminary incubation in sodium tetrathionate broth and in peptone water containing brilliant green in dilutions of from 1 : 70,000 to 1 : 1,000,000. Combination of these three methods was found to give the greatest efficiency.

The authors comment on the high ratio of non-clinical carriers to clinical cases. The reasons for the abrupt termination of the epidemic are not clear, as it is accepted that antibodies do not begin to appear in the serum until 5–6 days after the first immunising dose. No harmful effects appear to have been produced by immunisation of patients after exposure to infection. The carrier-rate was not appreciably influenced by immunisation.

30

BACTERIOLOGICAL OBSERVATIONS ON THE AIR OF OCCUPIED PREMISES. I. Air disinfection with hypochlorites. A simple practical method of disinfecting the air in occupied premises

by S. W. Challinor, *Journal of Hygiene*, **43**, 16–54, January, 1943

The crowded living conditions which may occur in wartime, for example in air-raid shelters, increase the risk of epidemics due to air-borne infection. For this reason the disinfection of air by a fine spray or " mist " of disinfectant (an " aerosol ") described by Pulvertaft & Walker (1939) has been further developed. The present author, of the Bacteriology Department in the *University of Edinburgh*, has studied the effect of hypochlorite disinfectants used in this way.

The experiments were carried out in an unventilated room of a capacity of 1,700 cubic feet (about 48 m.^{3}) occupied by from 14 to 17 men. The disinfectants used were (*a*) a 1·3 % suspension of bleaching powder (calcium chlorohypochlorite), (*b*) a commercial preparation of sodium hypochlorite in alkaline solution diluted so as to contain 1 % of hypochlorite. This solution contained about 3 times as much available chlorine as (*a*). The solutions were sprayed either through an atomiser which gave a mist (or " aerosol ") or through a " *Flit* gun " [*Flit* is a commercial insecticide] which gave a relatively coarse spray. Both were found effective.

The bacterial content of the air was sampled on blood agar plates through the " slit sampler " described by Bourdillon, Lidwell & Thomas (1941). The plate was rotated on a gramophone turntable while air was drawn over it through a slit 0·25 mm. wide × 27·5 mm. long × 3 mm. deep, the lower edge of the slit being 3 mm. from the surface of the agar. Air was sucked through the slit and over the surface of the plate at the rate of 1 cubic foot (0·0283 m.^{3}) per minute by the pump of a vacuum cleaner. The colonies on the plate were counted after incubation at 37° C. for 30 hours.

The number of bacteria in the air was found to fall immediately after spraying and to begin to rise again 15 minutes later. The reduction in the number of bacteria after one spraying with the sodium hypochlorite solution was of the order of 33 per cent., and the bacterial content of the air could be kept at a low level by repeating the spraying every 15 minutes. The concentration of hypochlorite solution in the air averaged 0·38 cm.^{3} per million cm.^{3} of air; it did not produce any significant irritation of eyes or nose, though the smell was perceptible. The bleaching powder suspension was slightly less effective than the sodium hypochlorite solution.

Tobacco smoke interfered considerably with the action of the hypochlorites and spraying was ineffective if the relative humidity of the air was below about 71 % at temperatures from 54° to 74° F. (12·2° to 23·3° C.).

The author considers the sodium hypochlorite spray a cheap and effective method of reducing the risks of air-borne infection in crowded rooms.

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31

STAPHYLOCOCCUS AUREUS IN THE MILK OF NURSING MOTHERS AND THE ALIMENTARY CANAL OF THEIR INFANTS : A Report to the Medical Research Council

by J. T. Duncan and J. Walker, *Journal of Hygiene*, **42**, 474–484, October, 1942

The authors, working in the pathological laboratories of the *Emergency Public Health Laboratory Service* in London, found *Staphylococcus aureus* in the fæces of six infants suffering from mild diarrhœa with green stools. Though no causal connection between the organism and the disease was found, either at that time or later, these workers thought it worth while to study the incidence of the organism in mothers and infants in two hospitals.

The mother's milk was sampled by cleaning the nipple with sterile water and gauze, expressing two jets of milk and then directing a third jet on to a throat swab without allowing the swab to touch the skin. In the infant the throat and rectum were swabbed. In all, 87 mothers with their infants were studied, in addition to 28 mothers whose infants had been still-born. The mothers with infants had *Staph. aureus* in the milk in 92·7 % and 80 % (two different hospitals) of cases; 91·5 % and 100 % of the infants had *Staph. aureus* in the throat and 74·4 % and 40 % in the rectum. In only 3 cases was the organism not found in either mother or baby. The growth from the milk was often very profuse. It seemed probable that the mother was usually infected from the baby, as:

(*a*) *Staph. aureus* appeared first in the baby's throat in 33 cases, simultaneously in mother and baby in 39 cases and first in the mother's milk in only 15 cases.

(*b*) Only 21·4 per cent. of mothers without babies had *Staph. aureus* in the milk.

(*c*) The colostrum of 8 women examined before parturition in no case yielded *Staph. aureus*.

The authors suggest that the throat infection is maintained in the hospital ward by passing from baby to baby and that the baby's throat infects the mother's mammary ducts.

All the staphylococci were grouped by metabolic and agglutination reactions. In one hospital 94·3 % fell into only two groups; in the other hospital no group predominated. Some minor septic lesions in mothers and babies

were caused by staphylococci of the same groups, but there was no important illness or epidemic due to *Staph. aureus* during the investigation, which lasted a year.

Staphylocoagulase reaction. Some staphylococci have the power to clot citrated plasma either by a free coagulase liberated into the culture medium or by the direct action of growing cocci. This clotting power has been regarded as evidence of pathogenicity (A. M. Fisher, 1936). None of the staphylococci examined in this work produced a free coagulase but many living cultures caused clotting. The authors found that the speed of clotting and the density of the clot varied with the dilution of culture and plasma. The test was conveniently carried out by titrating a series of diminishing concentrations of plasma against a uniform dose of staphylococcus culture (*e.g.* 1,000 millions of cocci per $cm.^3$). The end-point could be taken as either:

(*a*) the highest dilution of plasma in which a definite clot was formed, or

(*b*) the mixture which coagulated earliest; here the relation of plasma dilution to culture dilution was expressed as a ratio, and called the "*optimum* ratio" for clotting.

The authors suggest that clotting caused by growing cocci alone is a less reliable sign of virulence than clotting in which a free coagulase also takes part.

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32

A MEDIUM SHOWING A DISTINCTIVE GREEN COLOURATION WITH GROWTHS OF *C. DIPHTHERIÆ INTERMEDIUS*

by M. Gordon and C. Higginbottom, *Journal of Pathology and Bacteriology*, 54, 435–442, October, 1942

The introduction of blood tellurite agar media has resulted in a marked advance in the diagnosis of *C. diphtheriæ* and particularly in the differentiation of types. Nevertheless, difficulty still arises often in the examination of nasal swabs owing to the presence in the nose of certain diphtheroids. These produce on blood tellurite agar media colonies so closely resembling those of *C. diphtheriæ intermedius* as to be almost indistinguishable, and a simple method of differentiating between them is desirable. Cooper, Happold, McLeod & Woodcock (1935–36) observed that growths of *C. diphtheriæ intermedius* on heated blood agar often showed a slight greenish tinge. This feature was, however, too variable to be relied upon as a differential characteristic.

The investigation reported in the present paper was undertaken in the *Department of Pathology and Bacteriology* at the University of Leeds, at the suggestion of Professor J. W. McLeod, with a view to producing this greenish tinge more constantly, and thus evolving a medium which would be of practical value in diagnosis. It was shown that the first essential was a heated blood agar medium of a good "chocolate" tint. However, the heating required to produce this was found to have an adverse effect on some factor in the blood which promoted the production of the green colour. This factor was shown to be present in the serum but not in the blood cells. Unheated serum was therefore added to the heated blood agar medium.

A medium giving constant and satisfactory results was made up with a basis of agar broth (adjusted to pH 8·0), containing *Lab. Lemco* (a concentrated meat extract preparation), 1%; peptone (Parke Davis & Co.), 1%; sodium chloride, 0·5%; and agar powder, 2·5%. This was autoclaved and then heated with 10% of sterile defibrinated rabbit blood for ten minutes at 75° C., after which it was cooled to 50° C. and mixed with 15% of sterile rabbit serum before pouring as plates.

On this medium:

(1) The growths of one hundred strains independently classified as *intermedius* were markedly increased and appeared rich olive green, particularly in confluent growths. The green tinge was less well marked with isolated colonies after 24 hours' growth and was best seen by reflected light, but it became quite definite after 48 hours' growth.

(2) The nasal diphtheroids yielded much finer growths, greyish in colour and devoid of greenish tinge.

(3) The *mitis* and *gravis* strains yielded exceptionally heavy growths, the *mitis* being whitish, slightly tinged with pink, and the *gravis* a greyish-white.

The greenish appearance of *C. diphtheriæ intermedius* on the medium is not due to a pigment in the growth but to a discolouration of the medium, which becomes obscured by a heavy whitish growth after 48 to 72 hours' incubation. It differs from the green colour produced by streptococci and pneumococci on heated blood agar in that it is very superficial and shows no outward diffusion from the margins of the growth. It does not appear to be a peroxide effect as no blackening occurs with growths on benzidine blood agar.

The *serum factor* promoting the effect described is definitely thermolabile. Though only slightly affected by heating for 30 minutes at 65° C., its action is almost completely destroyed by heating for 30 minutes at 90° C. It is associated with the protein fraction of serum and is not present in the ether-soluble portion. It passes through a Maassen filter unimpaired. It is also present in human, guinea-pig, horse and ox sera, but the characteristic effect described is obtained best with fresh rabbit serum.

The authors have used the medium described in this paper for some months as a routine method of differentiating between nasal diphtheroids and the *intermedius* strain of *C. diphtheriæ*, and the results have been satisfactory. A plate accompanying the original article shows the appearances on this medium of subcultures of (*a*) six strains of *C. diphtheriæ intermedius*, (*b*) three strains of nasal diphtheroids, (*c*) a *gravis* strain, and (*d*) a *mitis* strain.

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33

SLIT-LAMP MICROSCOPE IN NUTRITION SURVEYS: OBSERVATIONS IN SCHOOL-CHILDREN

by J. H. Kodicek and J. Yudkin, *Lancet*, 2, 753–756, 26/12/42

This paper records the results of the examination of 496 elementary school children in Cambridge with the slit-lamp microscope. The first of the authors is Assistant Physician to the Eye Department, *Addenbrooke's Hospital*, and the second is Sir Halley Stewart Research Fellow at the *Dunn Nutritional Laboratory*, Cambridge. The slit-lamp microscope has recently been used for the detection in eyes of early signs of riboflavin and vitamin A deficiency. Although the authors are not able to indicate at the present stage the significance of the changes observed, the use of the slit-lamp for nutrition work is a recent development and they believe that the recording of the common types of findings may help in the adoption of a uniform classification and nomenclature.

Bessey & Wolbach (1939) showed that in rats a deficiency of riboflavin led to a vascularisation of the cornea. Vitamin A deficiency has long been known to produce keratinisation of the conjunctiva and the cornea. Recently various workers have suggested that the slit-lamp microscope might be used to detect early signs of riboflavin and vitamin A deficiencies. Kruse (1941) has listed a series of changes in the conjunctiva which he believes to represent progressive stages of vitamin A deficiency and Sydenstricker (1940) has described the engorgement of the limbic plexus and an increase in the capillary loops which eventually invade the cornea in progressive stages of riboflavin deficiency.

In detecting riboflavin deficiency the authors of the present paper took as abnormal only those eyes in which there was capillary invasion of the cornea, and they therefore adopted a severer criterion of abnormality than that used by Sydenstricker. By so doing they believed that only cases of true ariboflavinosis were included. A total of 19 of the 496 children showed corneal vascularity and the proportion was significantly higher in the older children—only 1·5% of children in the junior schools compared with 8% of those at the senior schools.

In attempting to find the early stages of vitamin A deficiency the authors have paid most attention to the corneal epithelium, as this is the region where vitamin A deficiency is known to be manifested. They classify the corneal epithelial changes into 5 groups:

1. Smooth, transparent conjunctival epithelium.
2. Transparent epithelium with superficial wrinkling.

3. More pronounced wrinkling.
4. Small islands with definite opacity.
5. Areas of opacity much larger.

The authors do not claim that these groups represent a continuous graded series but they think it very probable that they do. They do not claim that the corneal changes are necessarily due to vitamin A deficiency, but they find that they vary according to age, economic status and sex, being more common in the poorer class school than in the better class school, in boys than in girls, and in older than in younger children.

None of these slit-lamp findings described could be correlated with height and weight (or Tuxford's height-weight index), hæmoglobin levels, dark-adaptation, intelligence or educational attainment.

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34

VITAMIN C NUTRITION IN THE ROYAL NAVY AND IN A SECTION OF THE CIVILIAN POPULATION DURING WAR-TIME

by G. Z. L. McNee and J. Reid, *Lancet*, **2**, 537–540, 7/11/42

The occurrence of sore and bleeding gums in naval personnel attracted official attention in 1940, chiefly because these men were being diagnosed as scurvy or "sub-clinical" scurvy, on the hypothesis of a war-time diet deficient in vitamin C. The authors, working at the *Gardiner Institute of Medicine*, University of Glasgow, carried out an investigation on the state of vitamin C nutrition in the Royal Navy, chiefly by the use of the *saturation test* of Harris & Abbasy (1937). The subjects were 392 seamen (from destroyers and smaller craft), and 176 male civilians of similar age and social status who were fully employed in engineering were also investigated for purposes of comparison. This involved over 1,000 individual estimations.

The daily test dose was 700 mg. of pure ascorbic acid by mouth. Urine was collected from the end of the third hour to the end of the sixth hour and titrated with 2–6 dichlorophenol-indophenol. The test dose was repeated daily until there was a sharp rise in the excretion of ascorbic acid. Excretions of more than 50 mg. indicated "saturation"; 5–50 mg. "approaching saturation"; less than 5 mg. "incomplete saturation."

Results. In the Spring of 1941 the majority of naval and civilian subjects required 5 test doses for saturation. In the Autumn of 1941 the naval subjects required 3 and civilian subjects 4 doses. Capillary Resistance Tests (positive and negative pressure) showed no relation between the number of petechiæ induced and the saturation test results. Clinical examination of the mouth and gums of 118 of the sailors showed: British (72 subjects), oral condition moderate (5 with sore and bleeding gums); French (12 subjects), moderate; Canadian (13 subjects), good; Polish (6 subjects), good (1 with sore and bleeding gums); Indian (16 subjects), perfect. The Indians cleaned their teeth by their own method with a twig. Those with sore and bleeding gums showed average response to the Saturation Test, but the Indians with perfect mouths had lower reserves and a diet poor in vitamin C. The authors conclude that good oral hygiene is of major importance. A similar investigation was made on 9 civilians with genuine scurvy collected during the year in the wards of the *Western Infirmary*, Glasgow. None of these showed sore and bleeding gums in their edentulous jaws, and only 1 out of 5 examined showed abnormally low capillary resistance. Nevertheless all had had diets grossly deficient in vegetables and potatoes for at least 4 months.

The authors' results show that (1) scurvy cannot be diagnosed from sore and bleeding gums or from diminished capillary resistance; (2) in adults relying on potatoes or vegetables for vitamin C, a state short of "saturation" is the rule, although they remain in good health which shows no improvement after "saturation."

It is suggested that *in adults* ascorbic acid is concerned mainly with tissue repair and that the maintenance requirement for ordinary health and work is small and has not yet been accurately determined.

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35

CRITIQUE OF THE SATURATION METHOD FOR DETERMINING VITAMIN C LEVELS

by L. J. Harris, *Lancet*, **1**, 644–646, 30/5/42

The author, who is Director of the *Dunn Nutritional Laboratory* at Cambridge, points out that there have been many criticisms of the saturation method for assessing vitamin C deficiency, and he feels that those criticisms should be considered.

The saturation test for vitamin C deficiency is based upon the fact that the amount of a large test dose of vitamin C retained by the tissues is proportional to the pre-existing deficiency, which is revealed by the smaller amount excreted in the urine. The amount excreted can be estimated by titration of a sample of urine with the dye 2, 6-dichlorophenolindophenol.

The author specifies 12 objections which have been made to the saturation test at various times. These, and his comments, may be summarised as follows:

1. *The titration technique is not specific for vitamin C.* The technique is sufficiently specific to measure the relatively large quantities of vitamin C excreted in the urine in the saturation test without significant prejudice to the results by interfering substances.
2. *The standard of saturation is uncertain.* When saturation is actually attained in any individual there is an unmistakable sudden and steep rise in the excretion of vitamin C, hence it makes little difference which arbitrary figure is taken as representing the standard of saturation.
3. *After saturation, there is still a wide fluctuation of excretion of the vitamin.* The fluctuation of excretion does not in practice make it difficult to fix a lower limit for excretion, because the initial saturation level is usually fairly constant for subjects of the same weight.
4. *Individuals vary in their response.* Subjects kept at the same intake of vitamin C have actually shown less variation in excretion than might be expected.
5. *Other factors (fever, muscular work, kidney function) influence the excretion.* In all the conditions mentioned the tissues are depleted of vitamin C to a different extent and it would therefore be expected that the saturation levels should vary.
6. *Analysis of blood vitamin C is preferable to the saturation test.* Analysis of the blood vitamin C is no more accurate than the saturation method and the latter is more convenient.
7. *The requirement depends on the body weight or age of the subject.* If test doses are given in proportion to the body weight and the values for the excretions of vitamin C are reduced to a body weight basis, these variations due to weight and age are reduced to negligible proportions.
8. *The accepted standard for the requirement of vitamin C is unnecessarily high.* It matters little whether the standard for normal vitamin C intake is too large or small, as the values from the saturation tests still have considerable comparative significance.
9. *A subject may be well below standard yet still in apparently good health.* Even if the thesis is accepted (which the author does not do) that absence of scurvy means sufficient vitamin C, the saturation test would still be useful in determining how far a subject was from the scurvy level. Evidence from all human and animal experience, however, indicates that the amount of a dietary essential needed for normal health is greater than the bare amount needed to prevent frank deficiency disease.
10. *Saturation is not necessary for optimum nutrition.* The use of the saturation test for estimating vitamin C deficiency does not necessarily imply that saturation is desirable, but rats, which synthesise their own

vitamin C, are saturated with the vitamin. The same is true for guinea pigs in their natural state.

11. *Vitamin C is not stored in the body, therefore the term "vitamin C reserves" is misleading.* Whether one talks of "reserves" or "degree of saturation" matters little, since the object of the test is simply to appraise the previous level of intake of vitamin C.
12. *Presumably a subject can adapt himself to low or high levels of intake of vitamin C and his response to saturation tests will then vary accordingly.* This objection is chiefly theoretical, since in practice subjects are found to respond in proportion to their past intakes.

The author concludes finally that the urinary saturation test for estimating vitamin C "reserves" of the body can be regarded as reliable.

36

COMPARATIVE DIGESTIBILITY OF WHOLEMEAL AND WHITE BREADS AND THE EFFECT OF THE DEGREE OF FINENESS OF GRINDING ON THE FORMER

by T. F. Macrae, J. D. C. Hutchinson, J. O. Irwin, J. S. D. Bacon and E. I. McDougall, *Journal of Hygiene*, 42, 423–435, July, 1942

The experiments recorded in this paper from the Department of Nutrition of the *Lister Institute* and the School of Agriculture and Animal Pathology of the *University of Cambridge* had two objects: (*a*) to provide further information on the relative availability of the constituents of white and wholemeal breads, and (*b*) to find whether the fineness to which wholemeal flour is ground affects the digestibility of the bread.

The usual method of determining digestibility was used by the authors (*i.e.* subtracting the output in fæces from the intake and expressing the result as a percentage of the latter).

The authors point out that there are objections to this method, because some material is contributed to the fæces from the secretions of the alimentary canal and because 10–30% of the dry weight of fæces is made up of bacteria. To avoid these fallacies therefore it was necessary to plan experiments according to a suitable statistical lay-out. There were six subjects and each was to be given three treatments (white bread; wholemeal bread from medium ground flour; and wholemeal from fine flour). There were six possible orders in which these treatments could be given and one order was assigned to each subject at random. With this lay-out, the effects of periods, persons and treatments would be separated by the ordinary analysis of variance. The experimental period of feeding lasted seven days, and during this period fæces were analysed for nitrogen fat and crude fibre. The subjects of the experiment were all healthy young males leading fairly active lives.

The average digestibility of the three breads in the six subjects tested is summarised in the following table:

	Total Energy	*Crude Protein*	*Ether Extract*	*Crude Fibre*	*Total Carbohydrates*
White Bread .	96·1	91·1	80·6	65·8	98·7
Fine Wholemeal Bread .	86·9	85·3	76·2	14·0	88·6
Medium Wholemeal Bread .	87·1	85·7	73·2	9·7	88·9

In every case, therefore, the figures for average digestibility of white bread differed significantly from those for the wholemeal breads, and there was 10% more energy derived from white bread. The experimental subjects were unable to eat more of the wholemeal bread to make up for the difference in energy and the authors suggest that it is important to bear this fact in mind when considering the diet of heavy workers. There was no difference in the digestibility between fine and medium wholemeal bread.

37

DIGESTIBILITY OF NATIONAL WHEATMEAL

by H. A. Krebs and K. Mellanby, *Lancet*, 1, 319–321, 14/3/42

In this paper from the Department of Biochemistry of the *University of Sheffield* the authors refer to the opinion recently expressed by Wright (1941) that the use of an 85% extraction flour [*i.e.* a flour representing 85% of the whole grain] would result in a reduction in the quality and quantity of protein available for human consumption, because the higher extraction flour would not be as well digested as the pre-war white flour of 75°, extraction. As the higher extraction flour is now the national standard in Britain and no previous data had been published on its digestibility the present authors felt that this question should be investigated.

Experiments were carried out on 6 voluntary human subjects who lived under controlled institutional conditions and who conscientiously observed all their instructions regarding the diet and the collection of excreta. They were fed on a mixed diet containing 700–900 grams of bread, providing about 4,000 calories a day. Fæces and aliquot samples of food were analysed in weekly periods; 0·7 g. of carmine was used for marking the fæces. The white flour used in these experiments was of 75% extraction, while the national flour was of about 85% extraction and contained 0·45% of fibre. About 90% of the flour was eaten in the form of bread, the rest in the form of puddings, sauces and cakes. Digestibility in this paper is defined as the value of

$$\left(1 - \frac{\text{amount of food residue in fæces}}{\text{amount of food ingested}}\right) \times 100$$

The dry weight and nitrogen content of the fæces were determined. It was found that on an average 94% of the dry matter and 89% of the nitrogen of the national flour were digested. Of the 75% extraction flour 97% of the dry matter was found to be digested and it was calculated from the data published by Macrae, Bacon, Hutchinson & McDougall (1941) that 91% of the nitrogen is digested. The authors point out that the difference in the digestibility of the two flours is much smaller than has been suggested by Wright and that they are therefore unable to substantiate his objections to raising the extraction of wheat flour to 85%.

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38

PHYSICAL TREATMENT OF ACUTE WAR NEUROSES —SOME CLINICAL OBSERVATIONS

by W. Sargant, *British Medical Journal*, 2, 574–576, 14/11/42

Experience gained in the present war has shown that physical methods play an important part in any comprehensive scheme for the treatment and rehabilitation of patients with acute war neuroses. The aim of physical treatment is to build up the constitution so that unavoidable stresses are better tolerated by the individual. Over 3000 military patients, in addition to non-military cases, have had to pass through a limited bed accommodation at the *Emergency Medical Service* Neurological Unit of which the author is Deputy Director, and there has thus been a pressing need to find a means of accelerating processes of normal recovery so that patients may improve sufficiently to return either to readjusted duties in the Armed Forces, or to some useful civilian occupation.

Unparalleled opportunities of testing and developing such methods have occurred in the author's unit. Patients were received direct from the Dunkirk beaches, and other acutely ill Dunkirk patients were admitted, months or weeks later, after an interval during which their condition had often gravely deteriorated. During the aerial Battle of Britain and during the aerial bombardment of London, numerous other acutely ill patients were received who had broken down either in the Services or in the Civil Defence organisations.

The most important finding in these cases was the need for immediate first-aid treatment of the acute neurosis occurring in patients of previously good personality, and this should be applied within hours rather than days. The response depends not only on the speed with which the treatment is given but also on innate qualities of personality. Alcohol, paraldehyde, sodium barbitone and sodium amytal can all be used in large doses as a first-aid treatment to arrest acute panic reactions as soon as they occur. Sometimes intravenous injections of barbiturates may be necessary to obtain more immediate effects, and they may also be

used to help in the rapid abolition of hysterical conversion symptoms as soon as they occur. The drug is injected to produce a state of mental relaxation, and the patient is persuaded while under its influence to regain the function of the affected part.

Continuous narcosis is desirable if severe anxiety or hysterical symptoms have persisted for even a week or longer; by the end of this time physical changes will have become more pronounced and conditioned fears will have become firmly established. The aim of this treatment should be to produce 20 hours' sleep daily for seven to ten days.

A new form of modified insulin treatment (Sargant & Craske, 1941) has been used on patients who show anxiety and hysterical responses in a good previous personality and who have lost one to three stones (6–20 kg.) as a result of long periods of stress. Such patients may appear superficially responsive to psychotherapy but often relapse under further strain unless the physical deterioration from which they suffer has also been remedied. A dose (20–100 units) of insulin just insufficient to produce coma is given to the fasting patient in the early morning. Three hours later a cup of tea containing 2 ounces (56 g.) of sugar, and 12 ounces (340 g.) or more of potatoes (these are used to save sugar) is given. A full lunch is provided $2\frac{1}{4}$ hours later.

The treatment has been used in over 300 patients. Its object is to produce drowsiness and hunger. Appetite is often enormously increased, and second or third servings of potatoes are urged on the patient. In suitable cases, great improvement in weight and physical condition is obtained, and there is a parallel improvement in the mental state. The treatment is not effective in states of severe depression. On recovery the patients are sent to modified duties or some less exacting environment, as they remain conditioned to their past experiences and there is no evidence that the treatment alters their normal resistance to stress.

Convulsion therapy has been found useful for patients who are severely depressed, do not put on weight despite the modified insulin treatment described above, and who, if left alone, may have to wait many months for spontaneous recovery to occur, even if they are immediately discharged from the army or removed from stress. The author believes that 75% of patients with a good previous personality and genuine severe depression may be expected to benefit from convulsion treatment.

He concludes that methods of physical treatment may be valuable aids to shortening the period of total disability in patients with good previous personality suffering from acute panic states, acute anxiety states, anxiety hysteria, and states of depression. These methods must be employed in conjunction with the usual psychotherapeutic and environmental treatments. Clinical experience and discrimination in the selection of suitable cases is necessary if full benefit is to be obtained from the use of physical methods.

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39

EMOTIONAL AND COGNITIVE CHANGES IN THE POST-TRAUMATIC CONFUSIONAL STATE

by A. Paterson, *Lancet*, **2**, 717–720, 19/12/42

This paper is from the *Emergency Medical Service* Brain Injuries Unit at Edinburgh. The author points out that conscious activity in man comprises many different functions which must all be present before human behaviour can be said to be normal, and which can be eliminated selectively by the various types of brain lesion. This selective disintegration of mental activity and conscious behaviour depends on the site and nature of the lesion.

In normal speech there is a general background of syntax and grammar which is grossly impaired by lesions in the temporo-parietal area of the cortex, and this background is rendered inaccessible for the aphasic patient. Lesions of the occipito-parietal area give rise to acalculia, the system of arithmetical principles being inaccessible. Lesions somewhere in the region of the third ventricle are liable to disturb the wider background of spatial and temporal relationships. The same rule of breakdown and recovery after cerebral lesions applies to the other higher cerebral functions, memory and orientation, perception and imagination, and maintenance of emotional attitudes and stable behaviour patterns.

In the present investigation cases of gross confusion were studied in detail as they present the most complete breakdown of ordinary conscious activity and reveal it in its simplest form. The commonest cause of this breakdown in the author's cases was severe concussional brain damage. The stages in recovery from confusion indicate the way in which the complex mental processes become restored. By the psychiatric study of those cases from the earliest stages in a special unit, information is being acquired on their course, management and disposal. This psychiatric approach and its application to the study of disturbances of cerebral function is dependent on the concepts evolved by Hughlings Jackson, Henry Head, and their successors.

Goldstein accounts for the phenomena of mental disintegration by application of the figure and ground principles of the *Gestalt* School of Psychology. He regards confusion as the blurring of the figure with the ground. The present author suggests that restriction of the cognitive process to single aspects of the perceived situation is of primary importance in confusional states. The background at the same time becomes inaccessible. Recovery consists of a gradual widening of the conscious field with increasing accessibility of the background. Ordinary perception consists of an object of attention with at least two types of background giving it meaning, namely, the surrounding spatial setting, and past experience of that object. The latter underlies the process of recognition. The author cites four illustrative cases in which there was a gradual widening of the field of attention from gross confusional states to a residual absent-mindedness, which may be regarded as a mild form of confusion. Strong interest and emotion may also restrict the field of consciousness, thereby permitting concentration on the relevant details of the situation covering the interest or emotion.

The affective changes found in confusional states have tended in the past to be overlooked. These emotional changes are shown by the author to be analogous in nature to the cognitive changes. Emotional attitudes are isolated and often excessive, and the normal balance between emotional trends becomes upset. In the confusional state the restriction of the cognitive attitudes and the isolation of the emotional trends reinforce each other.

Alcohol tends to restrict cognitive ability and enhance certain emotional attitudes in the normal person. When mental functioning is already impaired by head injury this effect is strikingly exaggerated by even small amounts of alcohol. Fatigue and emotional stress also exaggerate mental impairment, causing amnesic phenomena or fugue states. Restriction and fixity of cognitive and emotional attitudes can also be demonstrated in the minor personality changes so often found after severe concussion. The background of conventional, social and other standards is cut off, and the basic emotional traits such as aggression or timidity are unmodified and therefore become exaggerated. Two such cases are cited in which severe concussional head injury produced a personality change which, it is suggested, might be described as a " caricature effect."

The author concludes by stressing the importance and practical value of the study of the whole course of the post-traumatic confusional state, especially with regard to the distinction between the true post-traumatic personality change and neurotic anxiety states.

40

POST-CONTUSIONAL HEADACHE

by E. Guttmann, *Lancet*, **1**, 10–12, 2/1/43

The author, who is neuropsychiatric research worker at the *Nuffield Department of Surgery*, Oxford, presents in this paper a study of the incidence of post-concussional headache in 200 consecutive cases admitted to the accident service of the Radcliffe Infirmary diagnosed as head injury. Not all these cases were available for this study, as five were wrongly diagnosed, eight died, and a few were unsuitable for other reasons. The occurrence of headache was noted at six stages, and for statistical purposes no distinction was made between mild and severe headache. All headaches were included, even if due to intercurrent disease.

As an indicator of the severity of the injury the duration of post-traumatic amnesia was used, assessed on discharge,

as suggested by Russell (1932). In 179 cases the findings were:

	Post-traumatic amnesia up to:	*Cases*
Group O	5 minutes	33
„ A	1 hour	85
„ B	24 hours	39
„ C	7 days	19
„ D	over 7 days	3

The presence or absence of headaches was recorded at the following six stages:

Stage 1: on admission or when first able to answer questions.
Stage 2: during stay in hospital.
Stage 3: on discharge from hospital.
Stage 4: when expected to be fit for work.
Stage 5: three months after accident (patients who had resumed work only).
Stage 6: six months after the accident.

The incidence of headaches (+) in the different groups and at the six stages is shown below:

	STAGE 1		STAGE 2		STAGE 3		STAGE 4		STAGE 5		STAGE 6	
Group	Cases	+	Cases	+	Cases	+	Cases	+	Cases	+	Cases	+
O	28	14	27	13	27	9	27	10	22	2	26	5
A	81	47	81	44	73	16	56	25	52	14	55	9
B	34	14	38	16	36	6	28	10	27	4	34	6
C	17	0	17	3	16	1	13	2	11	4	13	3
D	3	0	3	0	2	0	3	1	2	0	2	0
Total	163	75 46%	166	76 46%	154	32 21%	127	48 38%	114	24 21%	130	23 18%

The total number of cases under Stage 1 is only 163, because 16 of the 179 cases mentioned above were suffering from other injuries which distracted attention from the subject of this study. At Stage 2 there are 13 missing numbers, due to early discharge and absence of detailed case notes between admission and discharge. Missing numbers under other stages are attributable to similar accidental circumstances.

From the table it will be seen that on admission, or when first able to answer questions, 46 % of the patients complained of headache. While in hospital headache was present at some time in the same percentage. 21 % of the patients complained of headache on discharge from hospital. At the first follow-up appointment (*i.e.* at the time when the patients were expected to be fit for work), 38 % reported headache. Three months after the accident 21 %, and six months after the accident 18 %, complained of headache.

When the cases were classified according to the severity of the injury—indicated by the length of the post-traumatic amnesia—it was found that, up to and including the first follow-up examination, the percentage of headaches in the milder cases was persistently and significantly higher than in the severe cases. This difference disappeared three and six months after the accident. The clinical analysis of the cases with a history of headache showed that the patient's age was not an important factor. A considerable proportion of the patients had been suffering from periodic headaches all their lives. In the majority of the remaining cases, an obvious psychogenesis was present.

The author's impression, in the light of his findings, is that head injury is likely to produce headaches, but that only half of the injured notice or remember them. 80 % of the cases can be discharged from hospital free from complaints. Less than half of those discharged are left with some liability to headaches. The predisposition is psychosomatic—that is, psychological factors are as important in precipitating headaches as physical factors (stooping, heat, exertion). The author's impression is that they are even more important. Six months after the injury this predisposition still manifests itself in less than 20 % of the cases, and in some cases liability to headache in the history before the accident can be traced. In most other cases social and psychological factors either precipitate the headaches or determine the patient's attitude towards them.

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IMPLANTATION OF SEX HORMONE TABLETS IN MAN

by G. L. Foss, *Journal of Endocrinology*, 3, 107–117, March, 1942

In 1937 and 1938 Deanesly & Parkes of the *National Institute for Medical Research*, London, first introduced the technique of subcutaneous implantation of tablets of compressed crystals of sex hormones in animals. In March 1938 the present author began to carry out at the Gynæcological Department of the *Bristol Royal Infirmary* the implantation of tablets of sex hormones into women, in some cases to avoid repeated injections in long term therapy, but in other cases with the object of studying the absorption rates of the different hormones. Tablets of œstrone, œstradiol, testosterone, testosterone propionate and progesterone were implanted in different women. The clinical results were reported in an earlier paper (Foss, 1939). The present paper is mainly devoted to a consideration of factors influencing the rate of absorption of sex hormones administered by implantation.

The tablets used were compressed from crystals of pure hormones and were either flat disks or cuboids. They were weighed and then placed in the anterior abdominal wall through a $\frac{1}{2}$-inch (1·27 cm.) incision made under local anæsthesia with 2% procaine solution with adrenalin. The tablets were inserted into a small lateral pocket in the fat to one side of the incision.

After varying periods ranging from 11 to 362 days the tablets were removed under local anæsthesia by dissecting them out of the fat and fibrous capsule with which they were surrounded. They were then washed, dried and weighed to determine the amount of absorption which had taken place.

The author points out that the rate of absorption of hormones administered by this method may depend upon:

1. The size and shape of tablets.
2. The degree of compression of tablets.
3. The relative solubility of the hormone in lipoids.
4. The degree of tissue reaction around the tablets.

Tissue capsules formed around œstrone tablets were found to be thin and to show little granulation tissue. Capsules formed after implantation of tablets of progesterone, testosterone and testosterone propionate were thicker and more fleshy, showing more granulation tissue and giant cells. Capsules formed after œstradiol implantation occupied an intermediate position. A similar gradation existed between the absorption rates of these hormones, and the author believes there was some connection between these two observations. He agrees with Emmens (1941) that, whatever may be the mechanism of absorption, the surface area of tablets will determine the rate of absorption. If a tablet is not highly compressed it will rapidly become pitted and its surface area will thus be increased. The author believes also that the relative solubilities of these hormones in the body fat plays a part in determining absorption.

The mean values of percentage loss of weight of the tablets per day give a calculated life of about 550 days for œstrone, 260 days for œstradiol, 118 days for testosterone propionate, 85 days for testosterone and 76 days for progesterone. Œstrone, therefore, is much more slowly absorbed than progesterone.

Œstrone and œstradiol tablets were implanted in women for chronic conditions needing continued œstrogen therapy, *e.g.* leukoplakia, kraurosis vulvæ and menopausal pruritus vulvæ, climacteric symptoms and galactorrhœa. Comfort was maintained in only a small number of cases for a few months. The case of galactorrhœa was not improved by œstrogen implantation but the flow of milk was temporarily arrested by implantations of testosterone and permanently arrested by testosterone propionate. A male eunuch regained full sexual function for 3 weeks after implantation of testosterone. Climacteric flushes in a woman were also relieved by testosterone propionate, which, however, had no effect when implanted into an impotent man.

As surface plays such an important part in the rate of absorption of the hormone, the author points out that when a small dose for a long time is required, a small round tablet of hormone should be implanted. Where a higher level of

dosage for a relatively short time is required, large flat disks should be used.

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42

THE ENDOCRINE SYSTEM AND HAIR GROWTH IN THE RAT

by C. W. Emmens, *Journal of Endocrinology*, **3**, 64–78, March, 1942

This paper from the *National Institute for Medical Research*, London, opens with a review of previous and often contradictory observations by other writers on the effect of the endocrine organs on the growth of hair. Disagreement of findings is attributed to the variety of methods used for quantitative estimation of the rate of replacement of hair and the lack of a definition for the term " hair-growth."

The present author studied in all instances an area measuring 5 × 2·5 cm. on the flank of the rat. This area was shaved or clipped, or depilated with barium paste. Samples of the growing hair were plucked at intervals from the regenerating area (the fine undercoat hairs were excluded). A record of the extent of regeneration was also made periodically as very few rats grew a new coat over the whole of the denuded site. The first criterion of growth was the length of the hair, the second was the area of regeneration.

Preliminary tests were made with 40 rats from the Glaxo Laboratories' Wistar colony, in which both flanks were denuded of hair. It was found that growth of new hair was not affected by the method of depilation, the area depilated, the side of the body used, or previous depilation. Part of the denuded area commenced to grow immediately, but the remaining area did not grow any hair until between 11 and 18 days in adult rats. This second growth phase occurred earlier in immature rats. In coloured rats the rate of hair growth was much more variable than in Wistar-descended albinos. Hair grew more rapidly in male than in female rats, but castration had no effect on the growth rate in males. On the other hand, the rate of hair growth in ovariectomized females was equal to that in males. It was found that in rats which had been thyroidectomized when adult, the rate of hair growth was considerably reduced.

Injection of androgenic hormones had no effect on the growth of hair, but œstrogens retarded it considerably, particularly in males. Œstrogens also caused bare patches to persist on the shaved area. Injection of pituitary extracts gave variable results. When female rats were injected with saline extracts of female rat pituitaries their hair grew more rapidly. However, if the extract was made from acetone-dried glands, there was no effect. Even a saline extract of mixed (male and female) rat pituitaries had no effect on the growth of hair in male rats. Extracts of acetone-dried pig, ox, or horse pituitary glands had no effect on hair growth in either male or female rats, and a saline extract of fresh ox pituitaries had no effect on normal or castrated male rats.

Two other steroid hormones—progesterone and desoxycorticosterone acetate—were tested, but they had no effect on hair growth.

43

EARLY DIAGNOSIS OF PULMONARY TUBERCULOSIS

by R. R. Trail, *Lancet*, **2**, 413–416, 10/10/42

The author of this paper is Physician to the *Royal Chest Hospital* (London) and to the Surgical Unit at *Papworth Settlement*. He points out that, in spite of the technical advances of recent years, there is much to be done before the diagnosis of early pulmonary tuberculosis is achieved. Increased propaganda and improved dispensary facilities for diagnosis have not materially affected the stage at which the disease is diagnosed, and the majority of sufferers are therefore still unsuitable for modern methods of treatment.

The principal cause of the failure to diagnose tuberculosis at the early stage is that the doctor has had to wait until the patient consults him over symptoms, whereas it is well known that many cases of established phthisis are symptomless. However, there is sometimes a failure to diagnose tuberculosis when warning signs are manifest. These include pleurisy, persistent cough, indigestion, lassitude, fistula-in-ano, amenorrhœa and erythema nodosum. Similarly, there are physical signs present long before adventitious sounds are heard, for example the sternomastoid sign (tension of the homolateral sternomastoid muscle at its origin at the proximal extremity of the clavicle) and lack of movement. Careful physical examination may show that cases considered bronchitic are, from stethoscopy alone, clearly suffering from early active tuberculosis.

Aids to diagnosis are the erythrocyte sedimentation rate, exercise tests and sputum tests, but radiological examination in the hands of a chest physician or radiologist with specialised chest training is much superior to any other method. Radiography is a method which, even at its lowest valuation, is a visual indication of abnormality calling for immediate and strict investigation. The doctor can seek out the patient by this means, as proved by the growing experience of the examination of the supposedly healthy.

The author reviews the results in 30,000 men and 10,000 women in the Royal Air Force examined by mass radiography, using 35 mm. units. In this series the incidence of active tuberculosis was 0·22% for men and 0·38% for women. The figures for inactive tuberculosis were respectively 0·36% and 0·56%. The incidence of active disease was about 1 per 1,000 more for women than for men at the age group 20–24, while the incidence for women under 20 was more than double that for men. Similarly, for inactive cases, the incidence in women under 20 was four times as great as among men, and one and a half times as great in the age group 20–24. The percentages approximate in the age group 25–29. On the basis of the results obtained by this survey, the author estimates that there may be in Britain 15,000 cases of active pulmonary tuberculosis among the supposedly healthy in the age group 18–24 years.

Experience shows that some 25% more cases are found in the early stage of disease by mass radiography than by present civilian methods of diagnosis. While one radiographic examination is useful, it is no guarantee for the future and periodic examinations are desirable.

The author concludes with the recommendation that routine mass radiography of the civil population should begin at school-leaving age and be repeated annually until the age of 30 or 35 is reached.

44

THE USE OF SILVER NITRATE IN THE PRODUCTION OF ASEPTIC OBLITERATIVE PLEURITIS

by R. C. Brock, *Guy's Hospital Reports*, **91**, 99–109, 1942

The production of an artificial obliterative pleuritis is of considerable importance in the management of certain chest diseases, and the present paper describes experiences in the use of silver nitrate for this purpose. Adhesions between lung and the parietes may be needed (i) before lobectomy, (ii) to allow suction drainage of a tuberculous cavity, Monaldi's operation, (iii) to cure the condition of chronic or recurrent spontaneous pneumothorax, (iv) to relieve the condition of chronic recurrent idiopathic pleural effusion. The best method of producing pleural obliteration previously described is that of Bethune (1935)—" pleural poudrage "—in which iodised talc powder is blown on to the pleura through a cannula and under thoracoscopic control.

Silver nitrate has several advantages over Bethune's method, not the least being that its use is a simple bedside manœuvre and not even a minor operation. As a result of preliminary animal experiments and subsequent observations in man, the author recommends a 10% solution, the usual dose given being 0·5 cm.^{3} This is injected into the pleura with an all-glass syringe (to avoid precipitation of silver) after induction of a small pneumothorax, and as much air as possible is removed as soon as the injection has been completed.

As some immediate pain is caused it is advisable to give a preliminary injection of morphia. There is usually a slight febrile reaction lasting 3–5 days and a variable amount of effusion is produced. This and any remaining air should be aspirated so that the pleural surfaces are not kept apart and prevented from adhering. After 3–4 weeks, artificial

pneumothorax is again attempted, and if this is successful, a second injection of silver nitrate may be needed. Usually one dose is sufficient.

The author has used the method in 20 patients before lobectomy, with complete success in 15 cases and partial success in 2 others. Of these 17 patients, 13 had had one injection and 4 had had two. The adhesions found at operation are ideal, being soft and avascular but firm enough to prevent collapse of the remaining lobe.

Twenty patients suffering from chronic or recurrent spontaneous pneumothorax were treated by this method, and in every case the condition was cured. Thoracoscopy is done first to exclude a condition such as congenital cyst which would demand other treatment. The silver nitrate is then injected, and the gradual expansion of the lung is encouraged by aspiration of air and fluid. Among the chronic pneumothorax cases was one lasting 9 years, and in none was the duration less than several months. The recurrent pneumothorax cases had had many attacks, often bilateral. These cases are usually most difficult to treat and cause much disability, and the introduction of the use of silver nitrate provides a simple, safe and certain way to cure them.

The author does not suggest that silver nitrate is the ideal medium for producing aseptic obliterative pleuritis, but his results show that the principle of the injection of an irritant compound is sound. Further work is now in progress with the objects (*a*) of improving the technique of silver nitrate injection, and (*b*) of finding a compound which may be even better for this purpose.

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45

TRAUMATIC HÆMOTHORAX

by A. Tudor Edwards, *Lancet*, 1, 97–99, 23/1/43

The treatment of traumatic hæmothorax has long been a subject of controversy and it is natural that the experiences of war should throw new light on this problem. The author, who is Consultant Adviser in Chest Injuries to the Ministry of Health (*Emergency Medical Service*), has analysed the findings in 204 cases of traumatic hæmothorax treated recently in British Chest Centres. The patients were both military and civilian war casualties and only those cases in which the hæmothorax was the predominant lesion were included.

The most important problem is the prevention of sepsis. Of the 204 cases in this series, 40 became infected. With penetrating or perforating wounds caused by small missiles the incidence of septic infection was 22%, while with non-penetrating injuries 11% became infected. The latter figure shows that infection can reach the pleura from the lung or blood stream when the chest is injured, a factor which has previously been regarded as unimportant. The retention of effused blood in the pleura contributes to the production of sepsis. Such blood should be aspirated at once, and aspiration should be repeated on alternate days until the lung has expanded. At the first aspiration it is an advantage to replace the fluid with air, as this allows the pleura to be evacuated without distressing the patient and may help to prevent further bleeding by keeping the lung collapsed. At subsequent aspirations air should not be introduced since it is desirable to maintain as small a pleural pocket as possible in case infection should develop. Blood transfusion may be required if the patient is exsanguinated and very rarely it may be necessary to perform a small thoracotomy in order to evacuate large masses of clot from the pleura. Small retained foreign bodies, not more than 1 cm. in diameter, should be left alone as they do not increase the incidence of infection.

It was not possible to estimate the value of the sulphonamide drugs in this series, but they have been shown to reduce pleural sepsis after operations on the lung and it is therefore suggested that they should always be administered by mouth as early as possible in cases of traumatic hæmothorax. Regular bacteriological examinations of the aspirated fluid should be made, and if infection develops the dose of sulphonamide should be increased and regular aspiration should be continued until the fluid becomes definitely purulent. The empyema will then be localised and should be drained by rib resection at or near the angle of the ninth rib, unless it is encapsulated elsewhere. Closed intercostal drainage in the early stages is not recommended because of the dangers of infection of the tube track and leakage of air into the pleural cavity (which delays expansion). After drainage by rib resection, careful irrigation and the application of negative pressure will hasten obliteration of the empyema. Modern respiratory exercises are essential to restore full pulmonary function as soon as possible, and especially trained masseuses are now employed at all British Chest Centres. Finally, no empyema can be considered as healed until the cavity is completely obliterated, and the tube should never be removed before this stage is reached.

In the whole of the present series only 3 patients died, one after thoracotomy in the presence of infection, one from a severe crush injury, and one after hæmorrhage from a buttock wound. Thus the total mortality in this series, including the 40 infected cases, was one death—0·5%. In only two cases was there severe residual disability and 90% of those aspirated within the first 48 hours had no residual disability whatever.

These results appear to confirm the value of Chest Centres in which special surgical, nursing, and auxiliary services are available.

46

THE LOW-PRESSURE PHASE OF BLAST

by A. L. Latner, *Lancet*, 2, 303–304, 12/9/42

Previous investigators have attached much significance to the high-pressure component of the blast wave as the cause of blast lesions (Zuckerman, 1940). The low-pressure phase has been somewhat neglected, and has not been regarded as a factor which can be primarily responsible for the production of lesions.

The present experiments were carried out to determine the effects, if any, of exposure to low pressures of exceedingly short duration. Mice were used as experimental animals. They were placed in a small thick-walled glass chamber, which was then connected to a three-way tap by means of a thick rubber connection. The apparatus was so arranged that movement of the tap could place the mouse in communication either with atmospheric air or with an 8-litre bottle which was connected to a pump and manometer. The large bottle was evacuated of air as completely as possible and the tap was rapidly turned through 360° to return to its original position. This momentarily placed the small mouse chamber in communication with the large evacuated bottle and then returned it to its original connection with room air. A piece of gauze prevented the mouse from being sucked into the tap.

Death occurred instantaneously, or after a short interval, in approximately half the animals exposed in this manner. Post-mortem examination of the lungs always revealed hæmorrhagic areas, which were not as a rule symmetrically distributed. Occasionally, other hæmorrhagic lesions both intra- and extra-thoracic, were produced. Such lesions have been found in the pericardium, thymus, liver, large intestine, pancreas and fallopian tubes, and their presence shows that extrathoracic lesions produced by blast cannot be brought forward as evidence that the high-pressure component was the injurious factor.

Animals which recovered completely were killed with coal gas at varying intervals after exposure. The recovery process was found to conform closely to previous descriptions in human cases (Hadfield, 1941), even to the occurrence of greyish patches in the midst of hæmorrhagic areas. These areas showed pseudopneumonic mononuclear infiltration which was beautifully demonstrated by using McGregor's azan-carmine stain (McGregor, 1929).

The author concludes that exposure to a rapidly produced low pressure of very short duration is capable of producing injuries similar to those produced by explosion blast, and it may therefore be inferred that the low-pressure phase of blast may possibly have an importance greater than that previously attributed to it.

Discussing the mechanism by which the low-pressure phase produces its effects, the author suggests that the pressure changes of blast are not directly communicated to the inside of the lung, because of the relative narrowness of the trachea and the exceedingly short duration of the blast wave. Under these conditions the intrapulmonary pressure

would be greater than the outside pressure during the low-pressure phase of blast. The large area of body surface would make this pressure difference very effective. The resulting over-inflation of the lungs would tear some of the pulmonary capillaries and so produce hæmorrhagic lesions.

It seems possible that the lung lesions of blast are primarily due to over-stretching of the lung substance (1) during the low-pressure phase, by the mechanism already indicated, and (2) at the end of the high-pressure phase, by the elastic recoil of the thoracic wall occurring after compression. These factors would tend to be additive. As far as the author can ascertain from published work this suggestion has not previously been made. It would indicate a method of preventing blast injuries of the lung. Over-inflation should not occur if the chest were covered with a tight inelastic bandage or jacket.

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47

TREATMENT OF WOUNDS AND INFLAMMATION BY X-RAYS AND RADIUM RAYS

by N. S. Finzi and F. Freund, *British Medical Journal*, **1**, 34–36, 9/1/43

X-rays were first used in the treatment of inflammatory conditions over forty years ago, but this treatment has since been neglected. It is suggested that the chief reasons for this neglect are that the treatment has universal applications and is therefore regarded with some suspicion, that the use of X and γ rays in malignant growths has distracted attention from other uses, and that incorrect dosage was used.

The authors maintain that by the employment of very small doses it is possible to benefit almost every type of inflammation, both acute and chronic. Most cases respond well, but not all. One of the authors found that experimental wounds of the skin in rabbits heal much more quickly when treated with X-rays. Two photomicrographs accompanying the article illustrate a striking difference in the appearance of irradiated and untreated wounds. Experimental wounds of the rabbit cornea also heal with much less inflammation on the side treated with X-rays. Comparable results were obtained by irradiation of experimental fractures of the fibulæ of rabbits. Healing was more rapid on the treated side and callus was less in quantity and more heavily calcified compared with the control. It was also found that the reaction following inunction of tuberculin into the skin of the rabbit could be prevented by treating the area with X-rays soon after the inunction.

The range of dosage which will cause improvement is wide, but if really big doses are used the effects are reversed, inflammation is increased and necrosis may occur.

Surface wounds heal quickly after irradiation, with loss of pain and diminution of exudate; chronic ulcers become covered with healthy granulations and heal; in ununited fractures X-ray treatment will often induce bony union.

Skiagrams are reproduced of a whitlow with necrosis of the terminal phalanx where the whole of the bone rapidly regenerated after X-ray treatment. The authors refer also to the successful treatment of post-herpetic neuralgia by irradiation of the posterior root ganglia, and they claim that trigeminal neuralgia responds to irradiation of the Gasserian ganglion. As examples of acute inflammations suitable for irradiation the authors cite carbuncles, erysipelas, cellulitis, lymphangitis and gas gangrene. Among sub-acute and chronic inflammations tuberculosis, actinomycosis, septic fingers, osteomyelitis and many other conditions have been treated. X-rays are now often employed prophylactically in plastic surgery for the prevention of keloid. The value both in peace and war of a treatment which will shorten the period of incapacity by accelerating healing needs no emphasis.

The dose should be between 30 *r* and 80 *r*. The former or even less may be applied twice a week, and doses of over 50 *r* upwards once a week. All these are the estimated doses received by the lesion itself. The authors prefer a relatively high voltage with filtration, but the number of *roentgens* must be greater than when a lower voltage and filtration is used. In acute cases it is better to use smaller doses and repeat in three and then in four days. With chronic cases weekly treatments are sufficient.

The authors conclude by suggesting that there will be a wide extension of radiotherapy in the future.

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LOCAL CHEMOTHERAPY NUMBER

SPECIAL CONTRIBUTION

SPECIAL CONTRIBUTION

RECENT ADVANCES IN THE ANTISEPTIC TREATMENT OF WOUNDS

by LAWRENCE P. GARROD, M.D., F.R.C.P.

Bacteriologist to St. Bartholomew's Hospital
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The immense achievements of systemic chemotherapy almost overshadow all other forms of medical progress in the past few years. Yet it will not have escaped the notice of any acute observer that a similar revolution is now taking place in the sphere of local chemotherapy. Antiseptics have been out of fashion since the last war, when they were generally considered to have failed. The orthodox attitude to them has been that they do more harm to tissues than to bacteria, and many surgeons believed that they could neither prevent infection in a wound nor cure it: indeed, in view of this widely held belief it is surprising that antiseptics have been so generally used. Recent observations, of which the following is an account, have rendered this attitude untenable, and there is a prospect that local chemotherapy will improve to the same extent as systemic.

Local Sulphonamide Treatment

For five years after the introduction of the sulphonamides the nature of their action was unknown. German and French authors, including Domagk (1937) himself, hotly denied that they had any useful direct action on bacteria at all, and had this belief not been overthrown there would have been no inducement even to attempt their local application. We owe our present knowledge on this fundamental question to Fildes (1940) and Woods (1940), who showed that the action of sulphanilamide on hæmolytic streptococci is to prevent the utilisation of para-aminobenzoic acid, a previously unrecognised essential growth factor, and that the action of mercury perchloride on bacteria is of exactly the same nature. That this type of reaction wholly explains the action of sulphonamide compounds generally in all bacterial infections is beyond doubt: it is only necessary that there should be a certain excess of the drug over the amount available of the substance essential for growth, and bacterial growth will cease. Since the concentration of the drug attainable by local application is much greater than that produced in the tissues by systemic administration, the former method should succeed. That it does so is now a matter of general experience.

There are records of several earlier attempts to apply sulphanilamide locally, but the first systematic study of its action in wounds was made by Jensen, Johnsrud & Nelson (1939) who, by introducing quantities up to 15 g. into compound fracture wounds, greatly reduced the frequency of infection in them. To trace the development of this form of treatment since it was given a rational basis by the work of Fildes is unnecessary: it is now common practice, and has been found useful in the peritoneum, nose, ear and elsewhere, as well as in wounds. Preventive treatment, as would be expected, is much more successful than curative, and the conditions against which the safeguard afforded is surest are hæmolytic streptococcal infection and gas gangrene. Hawking's (1941) study of prophylactic effect in experimental gas gangrene gives valuable data on the persistence of the powder in the wound and the concentration attained, both of which depend on the solubility of the drug:

	Concentration in wound fluid	*Persistence*
Sulphanilamide	1500 mg. per 100 cm.^{3}	less than 1 day
Sulphathiazole	104 „ „ „ „	5–6 days
Sulphapyridine	42 „ „ „ „	7–10 days

Of these three compounds, sulphathiazole best combines adequate dissolved concentration with duration of effect. It is this persistent action, achieved by the use of a slowly dissolving solid, which secures effective antisepsis.

The success of this treatment has brought about a complete *volte-face* in the surgical attitude to antiseptics generally: scepticism has given place to receptivity, and where one method has succeeded, others both old and new are now given a fair trial.

Proflavine

Among antiseptics available as long ago as the last war, acridine compounds had a unique claim to consideration as wound prophylactics. Not only did they combine a powerful though slow action on bacteria with freedom from any gross toxicity to tissues, but they stood alone in having been shown capable of destroying bacteria in experimental wounds and thus preventing infection. The recent revival of interest in these compounds was assisted by Russell & Falconer's (1940–41) observation that a buffered isotonic solution of proflavine was no more damaging to the surface of the exposed brain than normal saline, whereas other antiseptics applied in the same way caused a severe hæmorrhagic necrosis. Proflavine was included in Hawking's (1941) study, already quoted, of the prophylaxis of experimental gas gangrene, and appears to have been at least as effective as sulphonamides. In the similar experiments of McIntosh & Selbie (1942) proflavine was distinctly more effective than sulphanilamide in preventing the development of *Cl. welchii* infections in mice. Although these recent studies have been concerned only with anærobes, proflavine is equally effective against pyogenic cocci, and there is no doubt that its introduction into a recent wound should be an efficient method of preventing infection generally.

Clinical evidence of its usefulness has been obtained not by prophylactic use but in the much more difficult sphere of treatment. Mitchell & Buttle (1942) [*see BMB* 57] report that the introduction of from 0·5 to 2 g. proflavine powder into intractably suppurating gunshot wounds is often followed by an abrupt cessation of the purulent discharge and rapid healing. Many of their 80 cases had previously had full courses of systemic or local sulphonamide treatment without benefit. It may well be asked why their sensational success should have been achieved with a class of antiseptic which failed to achieve any such striking effect in similar cases during the last war. There are two answers to this question, one of which is the choice of proflavine: the marked superiority of this compound over acriflavine was first emphasised by Albert, Francis, Garrod & Linnell (1938), and strikingly illustrated in the experiments of Russell & Falconer (1940) already quoted. The future of antiseptic treatment with acridine compounds lies with proflavine (2:8 diaminoacridine) and possibly 2:7 diaminoacridine (Albert, Francis, Garrod & Linnell, 1938) and 5 aminoacridine (Rubbo, Albert & Maxwell, 1942): the two latter, which have emerged from the extensive and outstanding work of Albert on the acridines as the most promising among his new compounds, have so far not received adequate clinical trial. The second reason for this success appears certainly to be the method of application. Flavines have never before been used in solid form, and by copying the technique of local sulphonamide treatment, a degree of penetration and persistence has been achieved which is unattainable in other ways. This method deserves general attention and trial.

Propamidine

Propamidine (4:4′ diamidinodiphenoxypropane dihydrochloride) is one of a series of aromatic diamidines recently introduced for the treatment of trypanosomiasis and other protozoal infections. That they also have a powerful action on bacteria was demonstrated by Fuller (1942), who tested a large number of these compounds on many bacterial species. Even the best of them have apparently no systemic effect on bacterial infections, but the local application of propamidine has given excellent results. The rationale of this treatment is explained by Thrower & Valentine (1943) and three succeeding papers in the same journal [*see BMB* 58] describe its clinical effects. Propamidine is applied to wounds in a concentration of 0·1 % in a water-soluble jelly base, the cavity being filled with this or the surface covered with a layer of it, which is then covered with vaseline gauze to prevent escape or evaporation. Application is renewed every two days and the treatment continued for not more than ten. The object is to overcome established sepsis, and this has been achieved when treatment with sulphonamides had previously failed. The scope and effects of propamidine treatment are thus almost identical with those of proflavine in the hands of Mitchell & Buttle (1942), and a deliberate comparison of the two methods would be most instructive. Much remains still to be learned about the action of propamidine on bacteria, its nature, velocity, limitations and variability with species. Existing information on the last point suggests that *Streptococcus pyogenes* is the most susceptible species among common wound invaders: *Staphylococcus aureus* is also susceptible, but less so, while *Proteus* and *Ps. pyocyanea* are resistant.

Biological Antiseptics

This term is applied to antiseptics produced by or extracted from living things, and although it embraces lysozyme and the maggot treatment of wounds, its most important examples are produced by micro-organisms themselves. Bacterial antagonism has been recognised for many years, and is due to the formation by some species of substances destructive to others. One of these is tyrothricin (separable into gramicidin and tyrocidine) extracted by Dubos (Dubos & Hotchkiss, 1941), from *B. brevis*. This substance is highly destructive to gram-positive cocci, and has been successfully used for the local treatment of infections, particularly streptococcal: according to Francis (1942) a sulphonamide-resistant strain responded to treatment with it.

In a class altogether apart stands penicillin. Discovered by Fleming (1929), and re-studied, purified and effectively applied to therapeutics by Florey and his co-workers (Abraham, Chain, Fletcher, Gardner, Heatley, Jennings & Florey, 1941; Florey & Florey, 1943), this astonishing substance presents at the moment the most acute problem in medicine. It is extracted from cultures of a mould, *Penicillium notatum*: the yield is very small, and substantial loss occurs in purification, so that large-scale production involves prohibitive expense. Its exact constitution is unknown and synthesis therefore not in sight. The pure product is non-toxic, exerts a systemic action, and acts on a wide range of bacteria. It is the only known agent which will control staphylococcal septicæmia, and it is effective in infection by sulphonamide-resistant streptococci and pneumococci. That it also has an efficient local action has been shown both by experiment and clinically: in McIntosh & Selbie's (1942) studies it proved superior not only to sulphonamides but to proflavine in preventing experimental gas gangrene in mice. If it ever becomes freely available it will doubtless take an important place as a local antiseptic.

Very many other moulds, particularly of the genera *Penicillium* and *Aspergillus*, have been studied from this standpoint. Raistrick, Smith & Oxford (1941, 1942) have obtained good yields of bactericidal extracts from a number of moulds, and in some cases determined their constitution and even synthesised them. These substances and the mould products obtained by Waksman & Woodruff (1942) and others are without exception less bactericidal and more toxic than penicillin. They are thus unsuitable for systemic use, but may have their uses as a local application.

Methods of Application

Next to the choice of an antiseptic, the method of applying it is the most important factor determining success or failure. Most antiseptics suitable for application to wounds act slowly; they do not kill bacteria outright, but either kill them in periods measured at least in hours, or merely prevent their growth. The antiseptic must therefore be maintained in the wound for hours and even days. This effect is achieved with sulphonamides by applying them as a solid, which undergoes slow solution. The use of proflavine in this form for the first time is unquestionably a major factor in the success achieved by Mitchell & Buttle. It has long been objected against the flavines that their affinity for fabrics is greater than that for tissues: a wet dressing soaked in a flavine solution retains it, and the antiseptic may make no contact at all with some parts of the wound. Irrigation, as usually practised, is only momentary. But to scatter the powder itself in the wound, and allow its slow solution in the wound exudate, is an entirely different matter. The solubility of proflavine is 1 in 300, which by analogy with the behaviour of sulphonamides according to their solubility should secure good persistence. It certainly does remain in a wound for days, perhaps also because it is less readily absorbed than sulphonamides. Acriflavine is probably too soluble for this type of use, besides being less suitable on other grounds. Free solubility used to be considered a good quality in antiseptics: it is no longer so from this standpoint. What is needed for application in powder form is an optimum solubility, which will combine adequate concentration with sufficiently long persistence.

The persistent action of propamidine is secured by filling or covering the wound with a semi-solid preparation of it, and sealing the surface with a waterproof dressing. This is reminiscent of Meleney's technique (Meleney & Harvey, 1939) with zinc peroxide paste, and technique rather than any special virtue in the antiseptic used may well be responsible for his success. Bunyan (1941) secures total and prolonged immersion of the wound in a solution of sodium hypochlorite by enclosing the whole area in the cellulose bag now named after him and running the solution through it. Here again is a method far superior to the Carrel-Dakin method of irrigation used in the last war: the difference is that between a rivulet and a lake. In fact all new methods of treating wound sepsis provide in some way for prolonged and uninterrupted action. We have learned the virtues of antiseptics largely by learning how to use them better.

The Sequence of Discovery

No one before 1935 could have predicted even in his moments of wildest optimism that the control of bacterial infection by chemical means would progress as it has in less than a decade. If he had ventured on such a prophecy, he would certainly have expected local treatment to be perfected first, and systemic—the much more difficult task of attacking bacteria in deeper tissues and even in the blood-stream—to be achieved later. Actually this order has been reversed: systemic sulphonamide treatment had been firmly established for several years before any attempt was made to improve the local treatment of infections. The incentive to re-exploration of this neglected sphere was the success achieved by local application of sulphonamides themselves. In a bare three years since this revival of antiseptic treatment began, three new agents have come into use which will overcome infections in which sulphonamide treatment has failed. What are the relative merits and proper spheres of solid proflavine, propamidine and penicillin, and perhaps of other agents yet to be discovered, can only be decided by much more extensive trials. What is quite certain even now is that wound infections can be prevented by antiseptics, and successfully treated by antiseptics when they occur. Chronic suppuration in wounds is no longer to be tolerated as a sometimes inevitable evil: it calls for active treatment by one of the methods which these recent studies have brought to light.

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Dr. L. P. Garrod is Bacteriologist to St. Bartholomew's Hospital and Professor of Bacteriology in the University of London. He has studied many aspects of antiseptic action, including, in addition to the surgical use of antiseptics, their action in selective culture media, assessment by in vitro tests, urinary and intestinal antisepsis, and the bactericidal action of gastric juice.

Professor Garrod has maintained for many years, in opposition to general surgical belief, that the application of suitable antiseptics is capable of preventing wound infections. Since 1931 (St. Bartholomew's Hospital Reports, 64, 85) he has advocated the use of flavines for this purpose. He is author of "Recent Advances in Pathology" (with G. Hadfield); "The Chemotherapy of Bacterial Infections" (Lancet, 1938, I, 1125, 1178); "The Action of Antiseptics on Wounds" (Lancet, 1940, I, 798, 845).

CHEMISTRY AND PHYSICS OF ANTISEPTICS IN RELATION TO MODE OF ACTION

by A. Albert, *Lancet*, **2**, 633–636, 28/11/42

In this paper from the Department of Organic Chemistry of the *University of Sydney*, Australia, the author attempts to relate the activity of antiseptics to their physical and chemical properties on the basis of contemporary knowledge of chemical and physical factors in antiseptic action. The following types of antiseptics are distinguished.

1. *Hydrogen and hydroxyl ions as antiseptics*

E.g. the use of ammonium chloride or sodium acid phosphate to render the urine acid and thus inhibit the growth of *Bact. coli.*

2. *Anionic and kationic types of antiseptics*

These were first distinguished by Stearn & Stearn (1924). They are salts in which one ion has much greater molecular weight than the other and they apparently form un-ionised complexes with portions of the bacteria. The *anionic antiseptics* are salts of acids of high molecular weight, *e.g.* common soap, calcium mandelates, acid fuchsin, etc. These react with a protein in the bacteria and there is liberation of the sodium or basic ion which tends to form sodium hydroxide. Hence the reaction proceeds only in the presence of acid, and in practice these antiseptics are useless in infected wounds, moderately useful for skin sterilisation and very useful in the disinfection of the urinary tract, provided that the urine is kept acid.

The *kationic antiseptics* consist of hydrochlorides, etc. of bases of high molecular weight, and they include the basic dyes (brilliant green and crystal violet), the acridine antiseptics and a special group of the colourless higher aliphatic amines (*e.g.* " zephiran ", " CTAB "). The basic part of the antiseptic combines with acidic groups in the bacterium and free acid is liberated. The action of these compounds is more powerful than that of the anionic type since (*a*) bacteria contain more acidic groups than basic groups, and (*b*) more strongly acidic groups (phosphoric) seem to occur in the nuclear apparatus and enzyme systems. Many compounds of this group are active as disinfectants for wounds and for skin. However, some chemical configurations appear more active than others.

The Stearns postulated that, within limits, the bacteriostatic power ought to increase with increase of the basic strength, because (*a*) stronger bases are more highly ionised, and (*b*) antiseptics derived from strong bases should form complexes with protein which are more resistant to hydrolysis. However, if the base is too strong, it does not produce unionised complexes so easily. The application of this principle to the triphenylmethane dyes (*e.g.* brilliant green) is difficult, as the free bases form tautomeric modifications which complicate measurements of the basicity.

The reason why some kationic antiseptics are ineffective against gram-negative bacteria may be partly explained in terms of basicity, since gram-negative bacteria such as *Bact. coli* possess relatively fewer acidic groups than gram-positive bacteria such as staphylococci. The acridine compounds, on the other hand, form a good example of the influence of basicity. In the series of mono-amino-acridines, investigated by Albert, Goldacre & Rubbo (1941), the strength of the antiseptic action is approximately proportional to the basicity of the compound ; but as postulated by the Stearns, the highly basic compound 2–8 diamino methyl acridine (acriflavine) is no more active than the moderately basic 2–8 diamino acridine (proflavine).

3. *Long-chain polar compounds*

These compounds (*e.g.* " zephiran ") which form a special group of the kationic antiseptics are aliphatic amines with a long side chain of 12–16 carbon atoms. The principal constituent of " zephiran " is lauryl benzyl-dimethyl ammonium chloride. At a surface, the molecules orientate themselves so that the carboxyl or amine group (the head) at one end is in the water, while the lipophilic side chain, or " tail," is repelled from the water. Accordingly these compounds are concentrated at the surface of the water and greatly diminish the surface tension. Such compounds appear to be attracted to the living cell and to become orientated on its surfaces.

4. *Phenols*

The mode of action of these compounds is rather obscure. Phenol itself has little action in lowering surface tension, but its activity in this respect can be greatly increased by inserting a hydrocarbon " tail " (as in " izal " or cresols) or by a combination of halogen and hydrocarbon " tails," *e.g.* chloroxylenol (as in " dettol "). The antiseptic action increases proportionally to the power to diminish surface tension. The author suggests that phenols are concentrated in surface layers and that under these conditions the hydroxy group acts like an acid. If this is true phenols are anionic antiseptics.

The disadvantages of surface-active disinfectants are (*a*) that wastage in wounds is great through adsorption on pus and other debris, and (*b*) that they are always injurious to delicate human tissues.

5. *Other chemical mechanisms*

Formaldehyde acts by combining with the free amino groups of protein ; the halogenating agents, *e.g.* iodine and hypochlorites, act partly by halogenating free amino acids and partly through a direct oxidising action. Some substances, *e.g.* hydrogen peroxide and permanganates, act as oxidising agents.

6. *Sulphonamides*

The mode of action of these compounds has been brilliantly illuminated by Fildes (1940), who postulated that sulphanilamide displaces an essential metabolite—*p*-aminobenzoic acid—from a bacterial enzyme. This mechanism constitutes a refined and specialised chemical attack on a specific functional unit of the bacterium, as opposed to the more generalised chemical activity of other types of antiseptics.

The author concludes by suggesting that the whole subject of the mode of action of antiseptics offers great scope for collaboration between the physical chemist, organic chemist, and bacteriologist.

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SULPHONAMIDES USED LOCALLY : Their Absorption from Serous Cavities and Wounds in Man

by F. Hawking and A. J. Hunt, *British Medical Journal*, **2**, 604–606, 21/11/42

The sulphonamides are generally accepted to be the most satisfactory compounds for prophylactic local application to contaminated wounds. Owing to the greater concentration achieved at the site of potential infection, they are more effective when inserted into the wound than when given by mouth. The relative value of the different sulphonamide compounds depends partly upon their bacteriostatic activity (sulphathiazole being the most active) and partly on their solubility. The more soluble compounds produce a higher concentration in the fluids of the wound, but they are absorbed more quickly, so that their action is less prolonged.

The authors report from the *National Institute for Medical Research* and *St. Bartholomew's Hospital*, London, a study of the rate of absorption from human operative wounds, but the work was interrupted before completion by the departure of one author for military service. The sulphonamides were inserted as powder (5–10 g.) into the wounds at the end of the operation, which was usually abdominal. The subsequent absorption was followed by taking blood samples at 6, 24 and 48 hours and by measuring the excretion of drug in the urine. The results varied greatly from case to case, and did not depend particularly on the site or nature of the wound. In 11 cases 5 g. of sulphanilamide was inserted. Taken as an average for the group, the daily excretion on the first two days was 1·1 g., after which only small quantities were excreted. The total amount recovered from the urine was 2·5 g., showing that much of the compound is lost in the body. The average blood concentration of free sulphanilamide was 3·2 mg. per 100 cm.^{3} at 6 hours, 2·7 mg. at 24 hours, and 1·0 mg. at 48 hours. Slightly higher figures were obtained when 7·5–15 g. was inserted. The authors conclude that sulphanilamide remains in the wound in appreciable amounts for not more than 2 days.

When 5–7·5 g. " hypoloid sulphanilamide L.S.F." (15% solution of sulphanilamide lactoside sodium formaldehyde

sulphoxylate) was inserted, most of the excretion occurred within the first 12 hours, indicating that the compound was rapidly removed from the wound and that it is not suitable for local application. Four cases were treated with 4 g. of micro-crystalline sulphadiazine inserted intraperitoneally. Most of the excretion occurred on the second day, but smaller amounts were excreted on the first and third days. The average blood concentration of the free compound was 9 mg. per 100 cm.^{3} at 6 hours, 5 mg. at 24 hours and 3 mg. at 48 hours. The clinical effects of this treatment appeared to be good, allowing for the grave nature of the cases, but in two patients who died from other causes on the eighth and tenth days respectively, small lumps of unabsorbed sulphadiazine were found in the recto-vesical fossa surrounded by adhesions and lymph ; histologically there was little evidence of irritation due to these deposits, but the authors nevertheless consider that sulphadiazine is not the best compound for intraperitoneal use owing to these residues. When a 30% sulphanilamide preparation in an oily base was spread on gauze and packed into wounds of small surface area compared with their volume, the absorption of sulphanilamide was much delayed and was incomplete even after 6 days. Animal experiments have shown, however, that there is a risk when inserting oily preparations into wounds, since most of the oils cause fibroblastic reactions if they become embedded in the tissues (Hawking, 1943) [*see also BMB* **51**].

One of the authors had considerable experience of the use of sulphonamides for wounds caused during air raids. When applied locally they appear clinically to have been of great value in preventing or diminishing the development or spread of infection, and the same has been true of cases in which the peritoneum has been contaminated in various ways. When given by mouth, however, sulphapyridine was not sufficiently active to prevent the development of gas gangrene in a clean wound of the leg two days after radical surgical excision with drainage, during which time full doses of the compound had been given. No general toxic effects after local application were observed in this series.

In view of their own observations and those recorded in the literature the authors recommend sulphanilamide, sulphathiazole, or a mixture of the two, as the most suitable preparations for local application, inserted as a powder or as a fine suspension in saline, *e.g.* micro-crystalline sulphathiazole. Since a case of tetanus recently occurred in London following the intraperitoneal insertion of unsterilised sulphapyridine, it is necessary to sterilise all powder used for this purpose [*see BMB* **54**].

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EFFECT OF SULPHONAMIDE PREPARATIONS ON EXPERIMENTAL INFECTED WOUNDS

by F. Hawking, *Lancet*, **2**, 507–510, 31/10/42

During the battles of modern warfare the orthodox surgical treatment of wounds, that is, operative treatment in a properly equipped theatre, is often impractical. Lt.-Col. A. J. Gardham has suggested in a private memorandum to the War Wounds Committee of the *Medical Research Council* that in these circumstances the wounds should be filled with a sulphonamide paste after only a superficial cleansing, and covered with an occlusive dressing which would remain in position for several days.

The present author has investigated this suggestion experimentally in rabbits at the *National Institute for Medical Research* and some aspects of this work have been described elsewhere (Fuller, Hawking & Partridge, 1942 ; Hawking, 1943). Experiments on the absorption of sulphonamides from various oily preparations showed that sulphanilamide is rapidly absorbed *in vitro* from aqueous preparations or from oil-in-water emulsions, but only slowly from water-in-oil emulsions or from oily bases ; however, when tested *in vivo* (by smearing the ointment over a superficial wound in a rabbit) sulphanilamide is absorbed from oily bases almost as rapidly as from watery bases. This failure of oily bases to delay absorption under the conditions *in vivo* is due to the fact that the ointment is present as a thin film, so that the surface is very large compared with its volume. A slower rate of absorption, and thus a longer therapeutic action in the wound, can be obtained best by using one of the less soluble sulphonamides such as sulphathiazole, or the still less soluble sulphapyridine or sulphadiazine (Fuller, Hawking & Partridge, 1942).

Another part of this investigation reported elsewhere in more detail by the present author (Hawking, 1943), was concerned with the histological reactions of the tissues around the wound to the various preparations. When oils are inserted into the tissues they eventually become encapsulated. Vegetable oils cause the least reaction, especially cottonseed oil, which appears to be completely inert, and which lies in the tissues with only a thin wall of fibroblasts around it. Other vegetable oils, such as arachis oil or linseed oil, cause a little more reaction. Mineral oils, *e.g.* paraffin, are surrounded by a curious foam-like tissue containing great numbers of vacuolated phagocytes ; this tissue has often been called a "paraffinoma." Animal oils excite the greatest reaction, especially cod liver oil. After several days in the tissue this oil becomes changed chemically and then causes the appearance of dense collections of giant-cells. Simple aqueous preparations of sulphanilamide or sulphathiazole excite a little inflammation at first but they are afterwards absorbed leaving a minimum of scar tissue.

The author confirmed that these histological reactions to the various preparations occurred in infected wounds, and he recommends that as a rule oils or oily preparations should not be inserted into deep wounds, unless it can be ensured that all the oil can be subsequently removed from the wound. This may be done by applying the oil on gauze, as in the well-known vaseline gauze. From the experimental evidence, it would appear that cottonseed oil is the least harmful and cod liver oil the most harmful.

The experiments on the therapeutic effect of various sulphanilamide preparations which form the main subject of the present paper were made in rabbits wounded in the thigh by inserting scissors through an incision behind the knee and slashing the hamstring muscles as far as the ischium. A small volume of a culture of virulent sulphonamide-sensitive streptococci was inserted ; this contained over 10,000 lethal doses of the organism. Then a standard quantity of the sulphonamide preparation containing 0·6 g. sulphonamide was squeezed into the wound, which was afterwards closed by suturing. The control untreated rabbits all died in 2–3 days with generalised streptococcal septicæmia. The survival of the treated animals was as follows :

(*a*) with a 15% aqueous solution of *sulphanilamide lactoside sodium formaldehyde sulphoxylate* (a soluble preparation issued by Burroughs Wellcome, Ltd.)	0 out of 4
(*b*) with 30% *sulphanilamide* in an aqueous base .	2 out of 10
(*c*) with 30% *sulphanilamide* in oil-in-water emulsion	5 out of 10
(*d*) with 30% *sulphanilamide* in oil . . .	7 out of 10
(*e*) with 20% *sulphathiazole* as a suspension of microcrystals in saline	10 out of 10
(*f*) with 8% *sulphadiazine* as a similar suspension	4 out of 5
(*g*) with *sulphathiazole* injected subcutaneously .	5 out of 5

At the same time, the absorption of sulphonamide from the wound was estimated by measuring the amount excreted in the urine. The order of the preparations arranged according to the slowness of absorption was found to represent also the order of therapeutic effectiveness, and the author concludes that any factor which prolongs the presence of sulphanilamide in a wound thereby increases its therapeutic efficacy. The superiority of the results with sulphathiazole and sulphadiazine may be due partly to their slower activities. In other experiments, treatment was delayed until 6 or 17 hours after the wound had been inflicted and infected. In these cases the therapeutic results were less good.

The effect of these preparations upon the wounds was also studied histologically and the results were similar to those which have been described above. The wounds which had been treated with microcrystalline sulphathiazole or sulphadiazine or with simple aqueous preparations of sulphanilamide were indistinguishable from the control wounds. Those treated with oily preparations showed all the fibroblastic and phagocytic reactions associated with the pure oils.

The author then considers, in the light of this experimental evidence and of such information as is available from the regions of warfare, the original proposal that wounds on the battlefield should be treated by insertion of a sulphona-

mide preparation. Although human wounds which have been excised heal more quickly than those which have received only sulphanilamide powder and dressing, the majority of such wounds do not reach the surgeons until 24 hours or more have elapsed. Under these conditions a simple dressing in the form of a sulphonamide preparation which could be applied by a medical orderly from a collapsible metal tube, would be of value in delaying the development and spread of bacterial infection. The best preparation to use would be the microcrystalline suspension of sulphathiazole (Chambers, Harris, Schumann & Ferguson, 1942). When this is not available, the next best would be a simple aqueous preparation of sulphanilamide, e.g. *sulphanilamide* 30 ; *triethanolamine* 0·33 ; *stearic acid, beeswax* and *wool fat* each 1·4 ; water to 100. This preparation would be less effective therapeutically than some of the others, but it would be cheaper and less harmful histologically. Oily preparations should not be inserted into deep wounds unless incorporated on gauze to ensure complete removal of the oil. For this purpose the author recommends *sulphanilamide* 10–30 ; *cottonseed oil* 30 ; *triethanolamine* 1 : *stearic acid* 2 : *cetyl alcohol* 1·4 ; *chloro-cresol* (as preservative) 0·1 ; water to 100 parts. If cottonseed oil is not available, arachis or castor oil may be substituted.

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THE VALUE OF LOCAL CHEMOTHERAPY IN WOUNDS AND BURNS

by D. N. Mathews, *Lancet*, **2**, 271–275, 5/9/42

The writer, who is at present a surgeon in the Royal Air Force, has made a study of the quantitative changes of bacteria present in a series of infected wounds treated with two of the sulphonamide drugs. Twenty neglected wounds and burns were given a daily application of either sulphanilamide or sulphathiazole powder followed by a dry dressing. At each change of dressing a small quantity of the exudate in the wound was removed and diluted in a pipette used for counting red blood corpuscles. Measured quantities of this fluid were grown on agar plates and colony counts were made. Para-amino benzoic acid was added to the culture media in order to neutralise the action of any sulphonamide that might still be present in the exudate (this procedure was adopted in conformity with the findings of Woods, 1940).

In every case there was a great reduction in the number of bacteria per cm.^{3} of exudate during the first few days following the application of the sulphanilamide. This reduction was seen in the numbers of hæmolytic streptococci and also other bacteria, for example, *B. coli*, *B. pyocyaneus*, staphylococci and diphtheroids. The bacteria never disappeared, and after a few days their numbers remained constant. This may be explained by assuming that the organisms became resistant to the action of the sulphonamides. The condition of the wounds rapidly improved and healing progressed.

The concentration of the drugs in the blood and the urine was also estimated by Marshall's colorimetric method. After 1·5 grams of the drug had been applied to a wound the blood concentration rose to a maximum with the first 24 hours and then rapidly declined. A concentration of 1·0 mg. per 100 cm.^{3} of blood was the highest level recorded. In the urine a concentration of up to 24 mg. per 100 cm.^{3} was found, and the author recommends that the urine should be examined for blood and casts in those cases which are subjected to prolonged chemotherapy.

In the light of his own experience and the published reports of other investigators in Britain and the U.S.A. the author concludes that the local application of sulphonamides to wounds is of great prophylactic and therapeutic value.

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[Another investigation on blood concentrations of sulphanilamide attained after local chemotherapy is reported in *BMB* **21**.]

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LOCAL CHEMOTHERAPY IN EXPERIMENTAL LESIONS OF THE EYE PRODUCED BY STAPHYLOCOCCUS AUREUS

by J. M. Robson and G. I. Scott, *Lancet*, **1**, 100–103, 23/1/43

Experimental work on the treatment of staphylococcal infections by chemotherapeutic agents has been hampered by the fact that the production of standard staphylococcal lesions suitable for testing the effect of various therapeutic measures has presented considerable difficulty. In the present paper from the Department of Pharmacology, *University of Edinburgh*, the authors describe a method which depends on the production of *staphylococcus aureus* lesions of the cornea in rabbits.

A 24-hour culture of the organism is injected into the cornea, thus producing a small blister under the corneal epithelium. Ulceration of the cornea, usually with hypopyon, results. Equal lesions can be produced in both eyes of any one animal. A technique is thus available for testing the value of chemotherapeutic drugs in the treatment of localised lesions. When the drug is applied locally to one eye in each animal the other untreated eye is used as control, thus largely eliminating the difficulties due to individual variation.

Definite beneficial effects on the development of artificially induced staphylococcal lesions were produced by the repeated local application of (*a*) a crude preparation of penicillin * in solution, and (*b*) 30 % and 10 % solutions of sodium sulphacetamide (albucid soluble). A 15 % solution of solubilised sulphathiazole (sulphathiazole sodium formaldehyde sulphoxylate) was less effective ; tyrothricin and 2·5 % sodium sulphacetamide were of little or no value. In all these experiments treatment was begun an hour after inoculation. When the treatment was begun 24 hours after inoculation little or no benefit was produced by the application either of penicillin or of 10 % sodium sulphacetamide. The application of penicillin eliminated the *staphylococcus aureus* from the flora of the conjunctival sac, but this was not achieved when 10 % sodium sulphacetamide was used. Commenting on the clinical implications of their work, the authors point out that the experimental findings indicate that the essential value of sodium sulphacetamide is likely to be prophylactic rather than curative. These experiments also emphasise the importance of early and adequate treatment (especially during the first 48 hours) in the clinical use of these drugs. One of their most important applications is likely to be in the first aid treatment of industrial injuries of the cornea, where abrasions, in the absence of effective prophylaxis, are liable to develop into septic and destructive lesions.

[A preliminary clinical report of the prophylactic use of sodium sulphacetamide solution in traumatic ulcer of the cornea in coal miners has now been published (Dickson, 1942).]

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STERILIZATION OF SULPHANILAMIDE POWDER

Medical Research Council, *British Medical Journal*, **1**, 263, 27/2/43

A report (*Lancet*, 1942) of a fatal case of tetanus, possibly due to infection from local application of sulphanilamide powder, emphasises the desirability that sulphonamides and their containers for local use should be sterile. It has been shown in animals (Welch, Slocum & Herwick, 1942) that when sulphanilamide powder contaminated with tetanus spores is implanted in the tissues the development of tetanus is not prevented. At a conference held between representatives of the *Medical Research Council* and the *Association of British Chemical Manufacturers* it was agreed that a large-scale method of sterilization of sulphanilamide powder as used by Hynson, Westcott and Dunning in the U.S.A. was suitable for adoption by British manufacturers.

For small-scale sterilization of existing stocks in hospitals and elsewhere, the conference recommended the following alternative procedures:

* [The bacteriostatic substance from *Penicillium notatum* discovered as the result of the early investigations of Professor A. Fleming in London and the subsequent work of Professor H. W. Florey and his co-workers at Oxford.]

1. Dry heat maintained at 150° C. for one hour in a paraffin bath, with the technique proposed by Berry (1942) as follows: " Use dry sterile cotton-wool-plugged test-tubes [about 12 × 2 cm. or smaller]. Half fill them with the dry powdered substance, using a powder funnel. Flame the upper portion of the tubes and replug with the sterile plugs. Immerse to within one inch of the tops of the tubes in a liquid paraffin oil bath and maintain at 150° C. for one hour. If the tubes are to be stored the plugs should be covered with cellophane or paper."
2. Dry heat maintained at 150° C. for one hour in an electric oven, with precautions to ensure even heating throughout.
3. Autoclaving in a dressing sterilizer by the technique and with the precautions proposed by Buckland (1942) as follows: " An autoclave with vacuum drying attachment (dressing sterilizer) is used and the container is a dry boiling-tube plugged with non-absorbent wool. The boiling-tube must be thoroughly dried, if possible in a hot-air oven. (1) The jacket pressure of the sterilizer should be ready at a pressure of 20 to 30 lb. per square inch [about 1·4 to 2 kg. per cm.^{2}]. (2) Allow steam at 20 lb. into the empty closed chamber of the autoclave and leave for five minutes. (3) Using the appropriate valves clear chamber of all steam and condensed water. This process has heated the chamber, and the boiling-tubes, loosely plugged with non-absorbent wool and containing the powder (in 5- or 10-g. batches), are now placed in it. They should be placed on their sides, with the powder spread over their full length, giving a thinner mass for the steam to penetrate. (4) Leave the tubes for 15 minutes in the hot chamber; this heats tubes and contents sufficiently to prevent condensation inside and on the powder. (5) Autoclave at 15 lb. for half an hour. (6) Clear the chamber of steam and any condensed water quickly, and allow vacuum of 10 to 15 inches (25–37 cm.) for 15 minutes. (7) Remove tubes from autoclave, place a tight sterile plug of non-absorbent wool on the top of the one already in, and cap tubes with a suitable paper—preferably cellophane. Caking does not occur. If apparent caking is observed, it is only present while the powder is still hot and, when cool, a tap on the side of the tube is all that is necessary to show the sterile preparation to be the desired soft powder."

A proviso should be added with each of these recommendations that a sulphanilamide powder, to be satisfactory for local application, should not cake or be more than slightly discoloured with any of the techniques proposed.

The recommendations of the conference related only to sulphanilamide powder, as the sulphonamide preparation most frequently applied locally. It may be mentioned, however, that the paraffin bath technique described by Berry is recommended by the author as being suitable also for the sterilization of sulphathiazole powder in hospital practice.

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EPILEPSY FOLLOWING APPLICATION OF SULPHATHIAZOLE NEAR THE BRAIN

by A. C. Watt and G. L. Alexander, *Lancet*, **1**, 493–495, 25/4/42

This paper comes from the *Brain Injuries Unit* and the *Wilkie Surgical Research Laboratory* at Edinburgh. The local application to the brain of powdered sulphonamides has been widely adopted in neuro-surgical practice as a prophylactic against infection. Among the sulphonamides used for this purpose by the present authors was powdered sulphathiazole, but it was found that a high proportion of patients developed epileptic fits and even status epilepticus from 2 to 6 hours after operation. In all cases which developed epilepsy the dura mater had been opened and the sulphathiazole had been applied in the frontal region. Experimental application of 0·14–0·23 g. sulphathiazole powder to the fronto-temporal area of the brains of cats (of 1·6–2·5 kg. weight) under intratracheal ether anæsthesia caused epileptic attacks in 3 out of 4 animals. Epileptiform attacks were also caused by application of sulphathiazole to the occipito-temporal region in 2 cats and to the lower surface of the frontal lobe in a further 2 animals. In 2 dogs the drug was applied in the middle fossa as far medially as the carotid artery and pituitary, and severe epileptic fits were evoked. Control experiments with sulphapyridine, sulphadiazine and sulphacetamide did not result in the production of fits. It was not thought necessary to perform similar experiments with sulphanilamide in view of the published findings of Russell & Falconer (1940) and Botterell, Carmichael & Cone (1941).

Application of sulphathiazole in the region of the posterior fossa caused a " cerebellar syndrome " in 3 cats tested, while comparable experiments with sulphapyridine in 2 cats were negative. The authors conclude that sulphathiazole should not be used locally in cranial operations. The epileptogenic properties of this compound do not appear to be shared by sulphanilamide, sulphapyridine, sulphadiazine or sulphacetamide.

[Confirmation of these observations has now come from the U.S.A. and it is evident that it is dangerous to apply sulphathiazole either on or near the brain.]

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[*Abstracts of the above papers are available on request*]

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THE PRESENT STATUS OF AMINOACRIDINE COMPOUNDS (FLAVINES) AS SURFACE ANTISEPTICS

by C. H. Browning, *British Medical Journal*, **1**, 341–343, 20/3/43

The war has given a tremendous impetus to the study of antiseptic control of wound infections. One of the interesting features of recent work by British investigators is the revival of interest in the aminoacridine compounds, of which acriflavine and its precursor proflavine (salt of 2 : 8-diaminoacridine) were introduced as surface antiseptics by the author of the present paper and his co-workers in 1917. This paper is a review, in the light of recent experience of the properties of the diaminoacridine antiseptics, by one who has for many years been an advocate of their use. An important characteristic of these compounds is that their action is intensified rather than reduced when the medium contains a high concentration (above 10 %) of serum. Another point of importance is that they are fixed by fabrics, and application on cotton dressings therefore results in a lowered concentration of the compounds at the site of action.

The systemic toxicity of proflavine is very low—a subcutaneous dosage of 0·2 g. per kg. body weight is required to kill 50 % of mice within 2–3 days. The equi-toxic dosage of acriflavine is 0·05 g. per kg. The results in man indicate that toxic effects of absorption from locally applied proflavine or acriflavine in the amounts normally used are not to be expected. Only very slight irritation of the rabbit's cornea is produced by 3 minutes' contact with 2 % proflavine solution or 0·6 % acriflavine, but the latter compound, like most other antiseptics, was found by Russell & Falconer (1940–41) to cause hæmorrhage and necrosis of cerebral tissue in 0·1 % dilution. Proflavine in 0·1 % isotonic solution buffered at a *p*H of 6·2 was practically harmless when applied to the exposed brain.

The evidence of different investigators as to the effect of diaminoacridines on leucocytes is discordant, and the author concludes that the results *in vitro* have been determined largely by the methods used by individual workers. There are also great discrepancies in tissue-culture investigations on the effect of flavines on cells.

A useful method of testing experimentally the value of drugs in the prophylaxis of wound infection is by treating recent wounds in guinea-pigs which have been inoculated with virulent *B. diphtheriae*. Brief washing of the wound with acriflavine solution (1 % to 0·04 %) 1–2 hours after inoculation regularly saved the animals' lives, while washing with saline solution, 1 % to 5 % phenol, and " bipp " (bismuth subnitrate 25, iodoform 50, liquid paraffin 25) usually failed. Recent wounds of mice inoculated with streptococci may also

be successfully treated with aminoacridine compounds. McIntosh & Selbie (1942) found that a well-tolerated dose (0·5 mg.) of proflavine injected locally was rather more effective than 80 times the weights of sulphanilamide or sulphathiazole in preventing death in mice inoculated intramuscularly with 100 lethal doses of *Cl. welchii*. Hawking (1941) also found proflavine effective in guinea-pigs.

However, it is difficult to produce artificially in animals the suppurating wounds met with in man, and final conclusions must therefore be drawn from well-controlled clinical evidence. Recently a series of cases has been reported from the Middle East [*see BMB* **57**] in which proflavine was used with great success in the novel form of a powder in the treatment of infected wounds.

Some retardation of granulation and healing may follow continued use of the flavines, and for this reason it may be desirable to change the treatment later.

The author concludes that the supreme advantage of the flavines is their " pickling " or " cold-storage " effect, which enables wounded men to be transported without changes of dressing with the reasonable probability that their wounds will remain *in statu quo ante* as regards infection.

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PROFLAVINE POWDER IN WOUND THERAPY

by G. A. G. Mitchell and G. A. H. Buttle, *Lancet*, **2**, 416–419, 10/10/42

In this paper two medical officers serving with the British Army in the Middle East report a clinical experiment on the treatment of wounds with proflavine (2:8-diaminoacridine sulphate) applied locally as a powder. Sulphonamide compounds have been extensively employed in the present war and have proved effective in preventing, controlling and eliminating streptococcal wound infections, but they have proved much less effective when organisms other than streptococci were present. Wounds of bone and joints infected with staphylococci, or mixed cultures of streptococci, staphylococci, and other organisms were often particularly intractable. As proflavine was known to be a powerful and relatively non-toxic bactericide it was decided to try this antiseptic in the treatment of such cases. Eighty patients were so treated, with encouraging results in almost every case.

After preliminary cleansing of the wound, the proflavine was applied directly in the form of powder. It was dusted over the entire raw area, and introduced into cavities by means of a small Volkmann's spoon or blunt dissector. The average amount used was 0·5 g., but less was sufficient for small wounds and the maximum amount employed at any one application was 2 g. The method was often combined with the closed plaster technique, and in cases where the wound was not so covered, dressings were performed every 4–7 days.

Proflavine applied in this highly concentrated form appeared to be active against all the ordinary pyogenic organisms, except *B. proteus* and *B. pyocyaneus*. Where staphylococci were present it proved more effective in controlling or eliminating the infection than any other available drug. The effect in drying up chronically discharging wounds was sometimes remarkable, and with one doubtful exception there was no evidence of delayed healing in any case. The authors do not recommend that proflavine should supplant sulphonamides as the routine prophylactic and therapeutic agents against infection, but they believe that it is well worthy of trial in cases where these drugs have failed, and especially if the infection is staphylococcal. A mixture of 2–5 g. sulphanilamide and 0·5 g. proflavine powder was used successfully as a local wound prophylactic, and the rationale of this combined treatment was that sulphanilamide would combat streptococci while the proflavine would destroy staphylococci.

Most patients found that proflavine powder used as a dressing was unirritating. A few complained of a slight burning or tingling which rapidly abated. No general toxic manifestations, such as skin eruptions, albuminuria, jaundice, nausea, vomiting, or headache were encountered.

In discussing the significance of their results the authors comment that acriflavine has always been the most commonly used member of the acridine groups of antiseptics in spite of the experimental evidence (Albert, Francis, Garrod & Linnell, 1938 ; Falconer, 1940 ; Manifold, 1941 ; Russell & Falconer, 1940–41) that proflavine is as effective and less toxic. It has also been shown that 2:7-diaminoacridine is even less toxic than proflavine, but the former compound was not available for clinical trial by the present authors.

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I. PROPAMIDINE IN CHRONIC WOUND SEPSIS: An Experimental and Clinical Study

by W. R. Thrower and F. C. O. Valentine, *Lancet*, **1**, 133, 30/1/43

II. PROPAMIDINE IN CHRONIC STREPTOCOCCAL INFECTION OF RAW SURFACES

by A. H. McIndoe and A. R. Tilley, *Lancet*, **1**, 136, 30/1/43

III. PROPAMIDINE IN BURNS

by G. H. Mosley and J. P. Bentley, *Lancet*, **1**, 138, 30/1/43

IV. PROPAMIDINE AT AN E.M.S. HOSPITAL

by F. Kohn, M. H. Hall, and C. D. Cross, *Lancet*, **1**, 140, 30/1/43

[The therapeutic properties of the diamidine compounds were discovered by King, Lourie & Yorke (1937). They reinvestigated and confirmed the claim that " Synthalin " was trypanocidal, but found that its action was direct and was not due to a hypoglycæmic effect, as had been suggested by Jancsó & Jancsó (1935) and others. Compounds related to synthalin were then prepared and tested for trypanocidal activity. Amongst these were some diamidines, which were shown to be very active. Aromatic diamidines, prepared in the research laboratories of *May and Baker, Ltd.* (Ashley, Barber, Ewins, Newbery & Self, 1942), were found to be effective in trypanosomiasis and in other protozoal diseases, such as leishmaniasis and babesiasis.

The anti-bacterial properties of the aromatic diamidines were then investigated and as a result propamidine (4 : 4′ diamidino diphenoxypropane) was tried in *Staphylococcus aureus* septicæmia. Treatment with this substance reduced the colony counts in blood cultures but did not cure the septicæmia. Meanwhile, it had been demonstrated that the action of the diamidines, unlike that of the sulphonamides, was not inhibited by para-amino-benzoic acid or by pus and tissue fluids, and that they did not adversely affect the activity of leucocytes. Consequently propamidine was tried in the local treatment of wound sepsis and burns.]

I. *Propamidine in Chronic Wound Sepsis*

The investigation of the anti-bacterial properties of propamidine and its use in the local treatment of chronic wound sepsis are described in this paper by W. R. Thrower, consulting physician to *May and Baker, Ltd.*, and F. C. O. Valentine, director of the Inoculation Department of the *London Hospital* and pathologist in the *Emergency Medical Service* (Ministry of Health).

Two methods were employed for determining the *in vitro* activity of the substance on several strains of *Staph. aureus* and a hæmolytic streptococcus : (i) the slide-cell * technique

[* The slide-cell technique was originally described by Sir Almroth Wright (1923). In this method, 2 microscope slides are separated by 5 narrow strips of vaselined paper arranged at intervals transversely to the long axis of the slides. By this means, the space between the slides is divided into 4 very thin " cells " or compartments, each of which has a capacity of rather more than 50 mm³. Cultures in blood or other fluid media can be incubated in these cells and the effects of bacteriostatic or bactericidal substances can be studied.]

which enabled a comparison of the efficacy of propamidine and sulphathiazole to be made, and (ii) a dilutional method in broth. The lowest concentration of propamidine inhibiting the growth of staphylococci with the slide-cell method varied, with different strains, from 1 : 128,000 to 1 : 16,000. Against 3 of the 5 strains, propamidine was more effective than sulphathiazole. Para-aminobenzoic acid, in concentrations which completely inhibited the action of sulphathiazole, had no effect on the anti-bacterial action of propamidine. With the dilutional method, slightly lower concentrations of the substance were found to be effective, as compared with the slide-cell technique. The minimal effective concentration for the bactericidal effect of propamidine did not differ significantly from that for bacteriostatic action.

Repeated *in vitro* tests of the effect of propamidine on the phagocytic activity of leucocytes showed that in a concentration of 0·1%, phagocytosis was practically unaffected, 0·2% reduced it slightly and 0·4% was inhibitory, but did not kill the leucocytes. There was no hæmolysis with concentrations up to 0·4%.

Further *in vitro* tests were made to determine the effect of pus on the anti-bacterial activity of propamidine. With pus containing large numbers of staphylococci, the lowest concentration to show a bactericidal effect was 0·025%, though when fewer organisms were present 0·006% was bactericidal. With pus containing hæmolytic streptococci, the lowest bactericidal concentrations, in two experiments, were 0·003% and 0·004%. It was concluded from these experiments that a concentration of 0·1% propamidine should have little effect on the activity of leucocytes in a wound, whereas 0·025% should have considerable sterilising power.

For clinical use propamidine was incorporated in a concentration of 0·1% into a watery methyl cellulose gel of strength 4·5 to 5%. The wound was cleansed with normal saline and the cavity was filled with the jelly to skin level, using a sterile spatula. No jelly was allowed to remain on the skin edges, as long contact tends to cause inflammation. The wound and surrounding skin were then covered with two or three layers of impermeable vaseline gauze and a thin layer of gauze or wool. On re-dressing, exudate and jelly were washed out with saline and fresh jelly was applied. Satisfactory results were sometimes obtained when dressings were carried out weekly, but usually they were repeated on alternate days, or even daily if there was much discharge.

About 50 patients have been treated by this method. The results show that full benefit is obtained in 10 days. In many cases the wound had been infected for months but there was rapid improvement after application of propamidine jelly. Concentrations of more than 0·1% proved unnecessary and tended to injure granulations. Cultures from the wounds indicated that the streptococcus was the first organism to disappear, followed by the staphylococcus. If bone infection or a sequestrum is present, sinuses may persist even though the surrounding tissues become healthy. After the dangerous organisms have been removed by the application of propamidine jelly, the final closure of the wound must be brought about by skin grafting or secondary excision, though spontaneous healing may sometimes take place.

II. *Propamidine in Chronic Streptococcal Infection of Raw Surfaces*

The authors investigated the value of propamidine in clearing up persistent secondary infection by a beta-hæmolytic streptococcus of open wounds or old burns in 11 cases at the *Queen Victoria Plastic and Jaw Injury Centre*, East Grinstead. The wounds were all granulating areas with loss of skin, in which healing was retarded or grafting made difficult by persistent streptococcal infection on the surface. The propamidine was applied in the jelly form in 0·1% concentration, and was renewed every 48 hours. Swabs were taken before, during and after 10 days' treatment. Three successive negative swabs were required before an area was considered free from streptococci.

In some cases striking clinical improvement took place in the wounds within 48 hours of starting treatment with propamidine, especially in recently infected cases. From 2 to 10 days were required for control of the streptococcal infection and steady improvement occurred during this time in all cases. Occasionally reinfection took place and a second course of propamidine was required. In one case in which more than 10 days' treatment was given mild irritation of the skin took place. The authors believe that the water-soluble jelly used may not be the best vehicle for propamidine, and investigations are now being made with a different base.

III. *Propamidine in Burns*

The authors of this paper have investigated the control of established sepsis in wounds and burns and the prevention of sepsis in fresh burns at the Burns Centre of a Royal Air Force General Hospital. Seven recent burns were treated from the start with propamidine, 5 cases had received other treatment for 3 days or more and 2 cases were treated in order to prepare infected areas for skin-grafting.

Fresh burns were cleansed with saline, and dead skin was removed. A preparation containing 0·1% propamidine in a "lanette" wax (partially phosphated stearyl and cetyl alcohol) base was then spread thickly over the burned areas and a sealing dressing of vaseline gauze was applied and held in place with bandages. At 48-hour intervals the dressing was changed in a saline bath. After 10 days, treatment was changed to sulphanilamide and tulle gras dressings, to avoid the possibility of necrosis of the granulations from prolonged contact with the propamidine preparation. For infected burns, 0·05% propamidine in a water-soluble jelly base was used, as this allowed better mixing of the drug with sloughs and granulations, though it was sometimes slightly painful. The authors believe that propamidine in the form of a 0·1% concentration in lanette wax base with 1% stovaine may prove to be an almost ideal first-aid preparation for burns. This cream is simple to apply and very soothing.

In burns treated with propamidine, separation of sloughs and epithelialisation were rapid, and this, together with the mobility of the affected part during treatment, led to a minimum of scar tissue and a very good cosmetic and functional result. In some cases, the infecting organisms had become resistant to sulphonamides but yielded promptly to propamidine. Streptococcal and staphylococcal infections were effectively controlled by propamidine, but *B. proteus* and *Ps. pyocyanea* were still present in cultures after treatment. Before grafting can be carried out these organisms must be eradicated by other methods. Propamidine should not be applied for more than 10 days at a time, but a course can be repeated, if necessary, after a period of other treatment.

IV. *Propamidine at an E.M.S. Hospital*

An account of the use of propamidine in 13 cases at an *Emergency Medical Service* hospital is given by the authors of this paper. Infected wounds were cleansed with saline and the discharge was examined bacteriologically. The surrounding skin was then dried and propamidine jelly was applied to the whole surface. In some cases of burns the compound was used in a lanette wax base. The whole wound was covered with vaseline gauze and then a thin layer of cotton-wool and a bandage. Wounds were re-dressed every 48 hours and not more than 5 times in any one course of treatment. Exudate from the wound was examined bacteriologically before each dressing. In burns no preliminary cleansing was carried out, except that any coagulum due to previous tannic acid treatment was removed with the patient under general anæsthesia. The propamidine jelly or lanette wax preparation was simply applied to the burned area. No debris was removed and no blisters were opened. Active movements were encouraged from the beginning.

The results obtained in these cases were very encouraging. Thiersch or pedicle grafting was possible much earlier than with any other previous method of treatment. In wounds where skin-grafting was unnecessary, the relative freedom from infecting organisms allowed much more rapid epithelialisation than usual. In burns, pain was diminished and where there was only blistering, healing was often complete in only ten days. In no case treated immediately with propamidine did infection take place. Separation of sloughs from wounds or burns did not seem to be more rapid than usual but scar formation was not increased.

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TREATMENT OF SUPERFICIAL TUBERCULOUS LESIONS BY LOCAL APPLICATION OF PROMIN

by W. H. Tytler and A. D. Lapp, *British Medical Journal*, 2, 748–749, 26/12/42

Experiments by the first of these authors, who is David Davies Professor of Tuberculosis in the *Welsh National School of Medicine*, had indicated that di-dextrose-sulphonate of diaminodiphenylsulphone (known as " promin " in the U.S.A., and to be known as " promanide " in Britain) had a decided inhibitory effect on the evolution of experimental tuberculosis in the guinea-pig, as reported by Feldman, Hinshaw & Moses (1940, 1941, 1942). Although the drug, administered internally, has given disappointing results in the treatment of human pulmonary tuberculosis, it was thought that it might usefully be applied locally to superficial tuberculous lesions, in which a sufficient concentration could be maintained without producing a toxic blood level and a resultant anæmia.

To reduce the rate of removal by absorption of the highly soluble drug, it was incorporated in a tragacanth jelly, of such stiffness that it could just be forced through a medium bore needle (18 SWG). Solutions containing 3·0% and 3·5% tragacanth were of suitable consistency. Varying concentrations of promin were tried and 5% was finally adopted. The jelly was applied to closed abscesses by injection, after aspiration of pus. Aspiration and injection of promin jelly were repeated when necessary. The jelly was applied to open sinuses by a fine catheter tied to the syringe, and the application was usually repeated daily.

The authors give details of 10 cases thus treated, of which 5 were closed abscesses and 5 sinuses (4 related to spinal caries and 1 to tuberculous peritonitis). In one patient three separate subcutaneous abscesses each healed completely within two weeks from the first injection. Other results were less striking but in general were considered as more favourable than might have been expected from orthodox methods. Abscesses remained flat after one or more treatments, or healed leaving fibrous residues. Sinuses decreased steadily in depth, and some were almost healed after two to four months' treatment.

The authors feel that the results justify more extensive trials, and they hope, in particular, to be able to develop this method for the treatment in the dispensary of tuberculous cervical adenitis with abscess formation, and thus to obviate the need for operative treatment in hospital.

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60

THE NATURE OF THE VALVULAR ACTION (PASSIVE O ENING) OF THE EUSTACHIAN TUBE IN RELATION TO CHANGES OF ATMOSPHERIC PRESSURE AND TO AVIATION PRESSURE DEAFNESS

by J. E. G. McGibbon, *Journal of Laryngology and Otology*, 57, 344–350, July, 1942

Active opening of the Eustachian tube by voluntary or involuntary muscular action has been investigated and described by many writers, but *passive opening*, and thereby passive " one way only " movement of air through the tube, is so commonly accepted that its apparent simplicity has given rise to scanty accounts of its mechanism. This phenomenon, however, is the immediate cause of aviation pressure deafness (aero-otitis)—a lesion which frequently occurs during loss of height when flying owing to failure or inability to open the Eustachian tube.

It is well known that as the extra-tympanic pressure decreases during ascent in aircraft, or during decompression in a chamber, egress of air from the middle ear through a normal Eustachian tube is easy and automatic. Armstrong and Heim (1937), who published a full account of the sensations experienced by aviators during flight, state that during decompression from sea-level pressure (760 mm. Hg.) the tympanic membrane gradually bulges outwards until at a pressure corresponding to 500 feet (152 m.) altitude (745 mm. Hg.) a " click " is heard and felt in the middle ear and simultaneously the membrane is observed to snap back to its normal position as air escapes, without any muscular effort, from the tympanum along the Eustachian tube into the naso-pharyngeal cavity. This passive opening of the Eustachian tube recurs on an average at each successive decrease of extra-tympanic pressure corresponding to an ascent of 435 feet (130 m.) irrespective of the curve of atmospheric pressures, and closure takes place again almost immediately, leaving a residual intra-tympanic positive pressure of about 3·6 mm. Hg.

During loss of height in aircraft or compression in a chamber the Eustachian tube behaves in an entirely different manner, for a normal tube does *not* open passively and air does *not* enter the tympanum without the intervention of muscular action or of therapeutic inflation. Consequently an extra-tympanic positive pressure develops which pushes the tympanic membrane inwards and invaginates it around the middle ear contents. This is often but incorrectly referred to as " retraction " of the tympanic membrane. The difference between the extra- and intra-tympanic pressures depends not only upon the amount of height lost but also on the curve of atmospheric pressures, *i.e.* the altitudes at which the loss occurs. Thus with a loss of 10,000 feet (3050 m.) from 30,000 feet (9150 m.) to 20,000 feet (6100 m.) altitude a difference of pressure of 123·6 mm. Hg. is developed. Whereas with a similar loss of 10,000 feet from 12,000 feet (3660 m.) to 2000 feet (610 m.) altitude a differential pressure of 223·4 mm. Hg. is effected.

The mechanism of passive opening and closure of the Eustachian tube can be demonstrated in the following simple manner: If a piece of Paul's rubber tubing 1 inch (2·54 cm.) in diameter and 18 inches (46 cm.) in length is fitted with a rigid mouthpiece and air is blown into it, the tubal lumen becomes patent and air escapes from its distal end. Blowing causes a condensation of air at the proximal end which travels along the lumen of the tube until it is dissipated by its exit from the distal orifice. This corresponds to passive opening of the Eustachian tube during ascent in aircraft.

If suction is applied at the mouthpiece the tubing will " collapse " so that no air can enter its lumen. This phenomenon may be explained by consideration of a rigid-walled tube with a constantly patent lumen. Suction at the proximal end of such a tube produces a rarefaction of air which progresses distally along the lumen, and until this rarefaction reaches the distal opening no air moves into the tube. There is thus a definite time-lag between suction at the proximal end and movement of air into the distal end. If rarefaction of air is produced by suction at the proximal end of a soft-walled tube its walls are immediately *pressed* together by the extra-tubal atmospheric pressure, as owing to the time-lag rarefaction is more rapidly neutralised in this manner than by movements of air into the distal end of the lumen. This closure is complete and it corresponds to the passive closure of the Eustachian tube which takes place during loss of height in aircraft.

By the use of a simple apparatus (illustrated in the original paper) which represents a tympanic cavity and Eustachian tube made to scale, the effect of atmospheric pressure changes may be demonstrated in a striking manner.

On decompression (ascent) the artificial tympanic membrane, which is made of thin glove rubber, gradually bulges outwards and then quickly returns to its normal position as air is obviously expelled through the artificial Eustachian tube. This sequence of movements of the " membrane " recurs at regular intervals and gives the impression of rhythmic pulsations.

During compression (descent) the tympanic portion of the " cartilaginous " segment (in the model, this portion is lined with lint) of the Eustachian tube becomes flattened and no air enters its lumen. The artificial drumhead is gradually pushed in until the invagination becomes so extreme that the stretched rubber almost obliterates the model middle-ear cavity, and this persists after ground-level pressure is reached.

These experiments with the model ear show that the initial changes which occur in the true middle-ear cleft as a result of variations of the atmospheric pressure may be purely mechanical and in no way physiological, and that the immediate cause therefore of the syndrome of aviation pressure deafness may also be purely mechanical. In some subjects the existence of an anatomical peculiarity or of some adjacent pathological condition may be a contributory

factor. The experiments explain also the common radiological finding in such cases of obstruction beginning in the tympanic half of the cartilaginous Eustachian tube.

Armstrong & Heim state that at an extra-tympanic positive pressure of 90 mm. Hg. or more the Eustachian tube "locks," as the muscles concerned with its opening are unable to overcome this force. The necessity of actively opening the tube or of auto-inflation during loss of height in aircraft to avoid this "locking" is generally recognised and practised by flying personnel. If, however, these methods are not adopted or fail, "forced ventilation" of the middle ear by Politzer's bag or by Eustachian catheterisation will frequently be successful. Forced ventilation of this type can take place only because the ostium of the tube, although varying in shape, is formed anatomically as an open funnel. If there were a true valve at the orifice, increased naso-pharyngeal pressure would merely augment the degree of closure.

Decompression in a chamber or ascent in aircraft if carried out early may also relieve the symptoms, as by these means the extra- and intra-tympanic pressures are equalised. If these latter therapeutic measures are employed re-compression or descent must be carried out cautiously and the tube must be actively and regularly opened throughout the period of increase of atmospheric pressure.

In conclusion, the author emphasises the advisability of early treatment, because experience has shown that the severity of the effects of decreased intra-tympanic pressures, which have been aptly compared to dry-cupping of the tympanic mucosa, is aggravated by the lapse of time.

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61

THE TREATMENT OF THE INJURED WORKMAN

by W. Gissane, *Practitioner*, **149**, 349–353, December, 1942

This paper deals with the social aspects of the subject rather than with technical procedures. The author is one of the leading British authorities on the rehabilitation of the injured industrial worker, and is Surgeon-in-Chief and Clinical Director of the *Birmingham Accident Hospital* and *Rehabilitation Centre*.

It is becoming generally recognised that the treatment of the injured workman is a social as well as a surgical process. Personal feelings, above all the will of the workman to get well, play a decisive part in treatment, and the retention of this spirit throughout the whole period of treatment is of primary concern to any organisation set up to treat the injured workman. The principles for efficient treatment were laid down by Sir Robert Jones at the end of the last war.

A special committee of the British Medical Association in 1935 and an Interdepartmental Committee of the Home Office and the Ministry of Health in 1939 unanimously advocated the following measures:

1. Segregation of patients to special treatment centres.
2. Unity of control throughout treatment by the same surgical team.
3. Careful after-care.
4. Rehabilitation.

The most economic method of treating the injured workman is to give the most thorough surgical treatment possible from the stage of first aid right through to the workman's discharge from hospital. Further, hospital treatment must be actively concerned with the process of rehabilitation, or reconditioning: that is, the process of preventing or restoring the loss of muscle tone, restoring full function of the limbs and maintaining the patient's general health and mental alertness, in addition to the surgical treatment of the injured part. At the end of properly planned hospital treatment, which includes rehabilitation within the hospital, the majority of injured workmen (about 80 %) are capable of returning immediately to their pre-accident job. For the remaining 20% of injured workmen, who, owing to the severity of the accident or to their resistance to treatment, are incapable of returning immediately to their pre-accident job, special Centres away from the hospital are being used in Britain. In these Centres, treatment is concentrated purely on reconditioning weak muscles and building up general bodily strength and mental alertness. The workmen are resident in the Centres, and their work is gradually increased until they are capable of doing a full day's work.

For many workmen with the less severe type of fracture of the limbs who have to spend some period in plaster casts and yet are capable of walking and doing some work, workshops are being provided within the factory where the men are usefully employed under medical supervision. These sheltered workshops not only provide the workmen with facilities for earning money to supplement their compensation pay, but they are also used at the end of hospital treatment to up-grade some injured workmen gradually until they reach their pre-accident state.

Since the war there has been an increase in the number of factory accidents, and the full treatment of these workpeople has become a problem of national importance. The increase of reportable factory accidents in 1941 over those of the pre-war year of 1938 is as follows: Adult males, 42%. Adult females, 192%.

Finally, to ensure provision for those whose injury has resulted in such permanent disability that they are not physically capable of following their trade, there are *Vocational Retraining Centres*, and in one such Centre 500 trainees have been returned to industry since 1935 and, in spite of grave physical disability, have been found capable of competing in certain types of work on equal terms with the able-bodied.

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BAGASSOSIS. AN INDUSTRIAL LUNG DISEASE

by L. I. M. Castleden and J. L. Hamilton-Paterson, *British Medical Journal*, **2**, 478–480, 24/10/42

Sugar cane from which sugar has been removed is called bagasse. It consists of fibre with 1% protein and 5–7% silica. Board is made from bagasse by crushing it into small fragments either under water or dry. After crushing the material is washed and remains wet until the finished board is dried in a press at 200° F. (93° C.). The dry board is then sawn and trimmed. Dust is present in the air of the factory (1) where the bagasse is crushed, (2) at the sawmill, where it differs from that liberated at (1) in containing no protein. Since the dry crushing process was begun cases of lung disease have occurred among the workers feeding the crushing machine.

Case 1

A labourer aged 19 began a cough with increasing shortness of breath after two months' exposure to bagasse dust. His previous health had been very good. On admission to hospital six weeks after his illness began he was extremely short of breath, cyanosed, and had the signs of bronchopneumonia in both lungs. Examination was otherwise normal. Sputum was scanty, viscid and sometimes blood-stained with no pathogenic organisms in it. The blood count was normal. X-ray confirmed the presence of a bronchopneumonic type of lung lesion. The disease did not respond to sulphapyridine but oxygen relieved his dyspnœa. There was a rise of temperature on a few days only in the course of an illness which lasted 7½ weeks and ended by gradual disappearance of dyspnœa with accompanying clinical and radiological signs of resolution. He eventually returned to normal health with complete resolution of the lung lesions radiologically.

Case 2

An engineer aged 31 whose health had been good had an acute illness described as pneumonia after six months' exposure to the dust. He recovered from this illness (which was similar to that of Case 1) after 10 weeks and returned to work. Two months after resuming work he began to have increasing shortness of breath. When he attended as an out-patient he had a kyphotic emphysematous chest with clubbing of the fingers and fine râles in both lungs. An X-ray showed a few apical scars and a little fibrosis in the right mid-zone. Five months later his shortness of breath was extreme. He would now collapse from the slightest exertion and was admitted to hospital.

On examination there was marked dyspnœa at rest with orthopnœa but no cyanosis. Clubbing of the fingers was now more definite. The chest was kyphotic and rigid, with

signs of consolidation at the left apex and râles throughout the left lung and at the right base. Physical examination was otherwise normal. A blood count showed an eosinophilia of 1122 per mm^3. but was otherwise normal. Sputum was viscid, mucoid, scanty, never bloodstained and contained no pathogenic organisms, yeasts or fungi. He was afebrile throughout his stay of 3 months in hospital during which time his shortness of breath decreased until he was able to be out of bed without distress. X-ray shortly after admission showed wide upper mediastinal shadow, irregularity of contour of right diaphragm with pleural thickening in the costophrenic angle and streaky opacities of fibrotic appearance in both lungs. He has continued to attend as an out-patient with further symptomatic improvement but with no change in either the physical signs or radiological appearances.

Case 3

A labourer aged 40 had cough and shortness of breath after one month's exposure to the dust. After transfer to another part of the factory his symptoms had improved.

On examination he was a little short of breath. The chest movements were poor with impairment of percussion note and diminished breath sounds at the left base. There were no adventitious sounds and an X-ray showed no lung lesion. A blood count was normal.

Case 4

A labourer aged 44 had increasing shortness of breath and a cough after 4 months' exposure to the dust. He was transferred to outdoor work with improvement of his symptoms. On examination there was moderate cyanosis with dyspnœa at rest. The chest showed an impaired percussion note at the right apex with diminished breath sounds and rhonchi throughout all areas of both lungs. Physical examination was otherwise normal. A blood count was normal. An X-ray showed a general streaky opacity throughout both lungs.

The clinical appearance of these patients suggested an acute inflammatory lung disease with urgent and extreme dyspnœa but little or no febrile reaction. Case 1 appeared to be a bronchopneumonia of unknown ætiology. Case 2 seemed to be suffering from pulmonary tuberculosis though this could not be proved. The common factor of the inhalation of bagasse dust led to further enquiry and it was found that a case similar in all respects to Case 1 had been described by Jamison & Hopkins (1941). These writers were able to grow a fungus from the sputum of their case which, like Case 1, recovered completely.

It appears that bagasse dust is capable of causing a pathological process in the lungs which may either resolve completely as in Cases 1 and 3 or progress to a fibrotic lesion as in cases 2 and 4. Since no pathogenic organism or fungus could be isolated from the sputum of these cases it seemed possible that an allergic factor might play a part in the disease. Extracts for skin tests were therefore made from whole bagasse in several solvents, that finally adopted being a normal saline extract of 20 grammes of coarsely crushed bagasse in 200 ml. saline with 0·25% tricresol added. After standing for five days with occasional shaking it was filtered through a Seitz filter. A control of normal saline with 0·25% tricresol was also prepared. All the extracts gave negative results by the scratch technique, but positive results by the intradermal injection of 0·2 ml. in cases 2, 3 and 4. The saline extract gave a skin reaction which attained a maximal area of 40 mm. in 36 hours. Seventeen normal controls gave a negative reaction to this test. A similar extract from dust at the sawmill gave negative results when tested on Cases 2, 3 and 4.

The acute phase of the disease may therefore be an allergic response to this saline-soluble antigen with or without an added infective factor. The nature of the chronic process is obscure. It might be (1) silicosis, (2) due to cellulose, (3) fibrosis occurring in tissues œdematous from the allergic phase. No opportunities for the study of the morbid anatomy of the condition have yet occurred.

The original paper is illustrated by 8 radiographs.

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NON-GONOCOCCAL URETHRITIS

by I. N. Orpwood-Price, *British Journal of Venereal Diseases*, **18**, 112–116, July–October, 1942

This paper was read at a meeting of the Medical Society for the Study of Venereal Diseases. Figures obtained after investigation of 500 consecutive patients suffering from a urethral discharge and attending the Whitechapel and *University College* Hospital Clinics (London) show the incidence of non-gonococcal urethritis amongst the civilian population to be 20% of all urethral discharges. As 80% of urethral discharges are gonococcal in origin, the diagnosis of non-gonococcal urethritis is usually by exclusion.

Of the aids to diagnosis, serum tests are of primary importance. The Wassermann Reaction should be performed as a routine in view of the possibility of an intra-urethral chancre. The Complement Deviation Test for gonorrhœa must be done, as hidden foci of gonococcal infection are often not demonstrable by the usual smears. The author believes that a *persistently* positive reaction, even in the absence of other evidence, is a definite indication of the presence of a gonococcal infection. A diagnosis of non-gonococcal urethritis, however, cannot be made on the strength of one negative reaction, but if it is persistent and is reviewed in conjunction with the clinical picture and other pathological tests, the reaction is of real assistance.

Cultures from the anterior urethra should in the author's opinion always be made, although if gonococci are not obtained not much information can be gathered from the organisms which are grown. Of paramount importance are vesicular cultures. This short term indicates that the material inoculated is obtained from the posterior urethra, prostate gland, and seminal vesicles by so-called prostatic massage. The author describes important details of technique, including the bacteriological examination by means of the oxidase reaction.

Care must be taken that the culture medium is suitable, and failures may be due to (*a*) poor quality of meat used in the preparation of broth, (*b*) inferior preparation of peptone, (*c*) unsuitable agar.

Direct smears from the urethra and prostate often yield valuable information.

The author concludes by emphasising that it is impossible to arrive at a diagnosis of non-gonococcal urethritis until the possibility of gonorrhœa has been excluded.

Corrections to BMB No. 1

BMB 15

(*i*) *The reference to the page numbers of the original should have been 44–85*, not *44–84*.

(*ii*) *In line 5 from the bottom, 60% should be 69%.*

BMB 21

In line 12, "usually 15 to 20 grams" is misleading. Of 41 cases in the series, only 9 received 15–20 grams. In 2 cases more than this amount (25 and 40 grams) was given, while less was given in the remaining 30 cases (14 cases, 1–5 grams; 12 cases, 8–10 grams; 4 cases, 12 grams).

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BRITISH MEDICAL BULLETIN

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The object of this Bulletin is to provide a guide to medical science and thought in Britain, and it consists mainly of summaries of a representative selection of British papers on subjects of medical interest. Any material appearing in the Bulletin may be published without fee, but acknowledgment of the source, by addition of the initial letters BMB followed by the serial numbers of the items selected, would be appreciated. The Bulletin is not distributed generally to the medical profession.

PUBLIC HEALTH

SPECIAL CONTRIBUTION

SPECIAL CONTRIBUTION

THE ORGANISATION OF A NATIONAL PUBLIC HEALTH LABORATORY SERVICE

by A. LANDSBOROUGH THOMSON, C.B., D.Sc.

Principal Assistant Secretary, Medical Research Council

I. The Situation before the War

Modern laboratory methods bring powerful aid to a Medical Officer of Health in the discharge of his responsibility for the control of infectious disease. In performing this important task he is clearly entitled to all the assistance that science can give; yet in actual practice he may count himself fortunate if he is able to call upon a thoroughly efficient public health laboratory service—staffed by trained specialists, adequately equipped and conveniently placed.

The difficulty, so far as Great Britain is concerned, arises incidentally from the way in which public health administration has developed. Executive responsibility rests primarily with local authorities, although general guidance is given by the appropriate departments of the central Government. The communities administered by these local authorities vary greatly in size and resources, ranging from large cities to small or sparsely populated rural districts. Each authority employs its own public health staff, and only the most important can afford to include in this a complete laboratory service.

Most local authorities are thus compelled to rely on such assistance as can be obtained from laboratories intended primarily for other purposes. Many university laboratories, for instance, undertake routine work for neighbouring local authorities, but this function is naturally subordinate to the claims of teaching and research. The work done is of a high technical standard; but it cannot easily extend to the provision of a complete service, including constant availability for personal consultation and for participation in field investigations. Similarly, many hospital laboratories make examinations for public health purposes, but their main work is of a different kind. They are interested in the individual case, with a view to its diagnosis and treatment, rather than in the herd from the standpoint of preventive medicine: their methods are those of clinical pathology, consisting largely of work which is not bacteriological in nature.

In other cases the Medical Officers of Health have to depend on laboratories run on commercial lines and often situated at a distance which precludes personal consultation and may involve serious deterioration of specimens in transit. Or again, the work may be done locally by persons who do not possess the necessary specialised training and experience. In the extreme case laboratory aid may be practically non-existent.

The remedy is to make provision on a broader basis by setting up laboratories to serve groups of local authorities and to deal with work sufficient in amount to justify the overhead cost of adequate establishments. The effectiveness of such laboratories will be further increased if they form part of a national service. Even an important local laboratory cannot cover the whole range of work with maximum efficiency, and it should therefore be in a position to refer particular types of examination to selected specialists elsewhere. Its staff cannot be large in number, and it should accordingly be able to draw upon a common pool of skilled personnel for substitutes to fill temporary vacancies or for reinforcement in times of exceptional local stress. Most important of all, the organisation of public health laboratories on a national basis is a means of providing an epidemiological intelligence network covering the whole country—for epidemics observe no administrative boundaries and the source of infection has often to be traced across the areas of many different local authorities.

Before the present war no such national service existed in Great Britain. A small central laboratory was maintained by the Ministry of Health, but its activities were restricted to certain special kinds of work. The Ministry also regularly collected epidemiological information relating to England and Wales—but not necessarily based on laboratory reports, from which the earliest and most precise information is often to be obtained; and from time to time it conducted special investigations. Similar functions were performed by the Department of Health for Scotland.

II. The Scheme brought into Effect at the Outbreak of War

It was in these circumstances that a Government decision was taken to include plans for an *Emergency Public Health Laboratory Service* among the preparations to be made in case of war. It was considered that the risk of serious epidemics might be much increased under war conditions, which were likely to include large movements of population and troops, interruption of normal services, and other factors. Many parts of the country, particularly in the south of England and Wales, were considered to be dangerously vulnerable owing to lack of adequate laboratory facilities for the diagnosis and control of infectious disease. It was therefore considered necessary to augment the existing arrangements by means of a special organisation which would fill the most important gaps.

Preparations were accordingly begun early in 1938. The planning and direction of the *Service* were entrusted to the Medical Research Council, acting in this particular matter on behalf of the Ministry of Health. The main scheme covered England and Wales, excluding the metropolitan area. Special arrangements were made for Greater London, and a separate scheme was organised by the Department of Health for Scotland.

Existing laboratory accommodation in universities, public schools and other institutions was designated for the purpose. Bacteriologists normally engaged in teaching and research, together with the staff of the Ministry of Health Laboratory, were allocated. Arrangements were made to borrow some of the necessary equipment, and the balance was purchased and stored. Provision for transport was also made.

As a result of these preparatory measures it was possible to mobilise the *Emergency Public Health Laboratory Service* immediately on the outbreak of war. Since then the scheme has been modified in various respects in the light of experience. The *Service* now consists of central laboratories at Oxford, Cambridge and Cardiff, and of smaller laboratories at Horsham, Winchester, Exeter, Ipswich, Norwich, Northampton, Leicester, Lincoln, Northallerton, Hereford, Carmarthen, Aberystwyth and Conway. In addition, a number of the principal permanent laboratories have been associated with the *Service*, so that they now contribute to the common pool of information and are able to call for special help when required.

To an increasing extent the Emergency Laboratories have been asked to undertake all the work of the local authorities in their area, and this is done in return for a contributory payment based on peace-time expenditure. As a matter of principle, these payments by local authorities are on a fixed annual basis, so that the amount of work demanded by Medical Officers of Health is not limited by considerations of false economy (as may happen where a fee is charged for every specimen). The laboratories also do work of relevant nature for military units.

The *Service* has not only aimed at a high standard of laboratory work, but has made a special feature of the availability of the staff for personal consultation by Medical Officers of Health and for participation in field inquiries. The fact that the laboratories form part of a single organisation has made it possible to develop a system whereby they refer particular kinds of work to specialists elsewhere within the *Service*. It has also facilitated the transference of personnel to meet changing requirements. The associated as well as the constituent laboratories have kept the headquarters of the *Service* informed on matters of epidemiological interest, and have thus greatly assisted the co-ordination of efforts for the control of outbreaks affecting wide areas.

An example of co-ordinated laboratory and field work may be given. The occurrence of several scattered cases of typhoid fever in a certain county was investigated by one of the Emergency Laboratories, and the opinion was formed that the infecting agent had probably been carried by milk. Although most of the patients had been supplied from different dairies, all these dairies had drawn some of their milk from a particular wholesale depot. Inquiry showed that the milk coming into this depot was derived from four different sources. One of these, a group of farms in another county, came especially under suspicion, but inspection of each of the farms failed to reveal the presence of anyone with a history of typhoid fever. The quest for the original source of infection was thus held up for the time being. One point, however, was established: the strains of typhoid bacilli isolated from the patients were referred to a specialist attached to the headquarters of the *Service*, who found that all these strains belonged to a single bacteriophage type, D4, which had not previously been encountered in Britain. This left little doubt that all the patients had been infected from the same original source.

Months elapsed before a further group of cases occurred, this time in a different part of the county in which the first outbreak took place. It was found that the dairy supplying the patients had received milk from the same wholesale depot as before, and again the organisms isolated from the cases belonged to the D4 type.

The clue to the puzzle was provided a few months later, when a single case of typhoid fever occurred in the other county from which some of the depot's milk supply came. Inquiry into the source of infection in this case showed that the patient had until recently been employed as a milkman at one of the farms of the group that had been under suspicion a year earlier. A full investigation at this farm led to the discovery that the owner, although his medical history had not given rise to suspicion on the former occasion, was in fact a chronic typhoid carrier. It could therefore be concluded that, through faulty personal hygiene, he had occasionally infected the milk which he had been sending to the wholesale depot. Thus, the co-operation of several laboratories with each other and with field investigators led finally to the detection of the distant source responsible for the outbreaks.

A different kind of co-operation is exemplified in measures which were taken with regard to a certain foodstuff of national importance that was being introduced into this country. Preliminary bacteriological examination by the Government department responsible for distribution of this foodstuff raised some doubt as to its wholesomeness for human consumption, and there was, accordingly, urgent need to examine numerous samples of the product on its arrival at the ports. The *Emergency Public Health Laboratory Service* was approached, and arrangements were at once made for the distribution of samples among about fifteen laboratories and for the collection of their reports at a single centre. In this way the supply of the foodstuff was kept under constant supervision. Defects in its quality were found, and as a result the authorities were able to arrange for measures in the country of origin which led to an improvement in the method of production and to the material being made more wholesome for human consumption.

III. The Future

The *Service*, although still on an emergency basis, has become an integral part of the public health organisation of the country. Medical Officers of Health in areas which were formerly poorly served appreciate the facilities which are offered, and there has been wide recognition of the value of a service organised on the lines which have been described. Hopes are therefore entertained that these emergency arrangements will be succeeded by a permanent system of a similar kind after the war. Although official decisions on this point have not yet been taken, there can be little doubt that improved provision for public health laboratory and epidemiological work will form an essential part of the extended medical services which are now being planned.

The benefits which may be expected are by no means static but should be cumulative in effect. An efficient laboratory service is not merely an instrument of routine but also a weapon of research. Experience has shown that organised investigations into epidemiological problems are capable of yielding important additions to general knowledge as well as information of immediate utility. The function of such a service is, therefore, not only to apply existing knowledge but at the same time to increase that knowledge and thus constantly to improve and extend the methods of preventive medicine.

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Dr. Landsborough Thomson has been a member of the Medical Research Council's headquarters' staff since 1919. *During the present war, and in the period immediately preceding it, he has been specially concerned with the administration of technical services which the Council has undertaken to direct, as an emergency measure, on behalf of the Ministry of Health.*

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THOUGHTS ON THE ORIGIN OF INFLUENZA EPIDEMICS

by C. H. Andrewes, *Proceedings of the Royal Society of Medicine*, 36, 1–9, November 1942

In spite of the great amount of work on influenza which has been done in the ten years since the first strains of the virus of epidemic influenza were isolated by Andrewes, Laidlaw & Smith (1934), many problems remain unsolved. In a stimulating presidential address delivered before the Section of Pathology of the *Royal Society of Medicine*, Dr. C. H. Andrewes of the *National Institute for Medical Research*, has reviewed the present position and put forward ideas which might explain some of the apparent inconsistencies in the behaviour of epidemic influenza. The published account of this address by such an authority on the subject deserves the earnest consideration of all who are interested in this important disease. Such a paper cannot be adequately summarised and only the main points can be mentioned here.

Andrewes draws attention to the fact that while the original viruses isolated from epidemic influenza, and now labelled influenza A virus, have been responsible for most of the widespread epidemics, the more recently identified B virus has also been isolated from quite a number of epidemics. It has been suggested that B virus behaves rather like an endemic virus with occasional outbreaks. In some outbreaks, however, cases occur in which neither A nor B virus can be isolated and these have been provisionally labelled influenza Y. Such findings may suggest that epidemics are caused by a number of different viruses, only two of which have yet been recognised. Andrewes, however, thinks that there may be more unity in influenza than such a view indicates.

Even in epidemics due to influenza A virus there are differences in the properties of the strains of virus recovered, not only in their antigenic structure and rapidity of spread in man, but also in their adaptability to laboratory animals. Andrewes tabulates variations in virus strains noted since 1933. In Britain, influenza A is prevalent only every other year, and during epidemics, subclinical infections appear to be common. Between epidemics, however, the virus apparently disappears. The work of Shope (1942) suggests that between epidemics of swine influenza the virus survives in lung worms and earth worms, and in the pig itself. While Andrewes thinks that a similar helminth reservoir of human influenza A virus is unlikely, Shope's work has shown that an influenza virus can survive in a masked form; it seems not unlikely that human influenza virus can exist in an occult form, perhaps in human beings.

With regard to antibodies in relation to immunity, it has been shown that the presence of potent antibodies in a person's serum only diminishes to a limited extent his liability to infection.

To find a solution for these various difficulties Andrewes postulates the existence of different grades of influenza virus. Grade I, the basic influenza virus, would resemble the degraded forms of many bacteria lacking a familiar antigen; it would lack the power to cause symptoms or stimulate the formation of A antibodies in man or to infect laboratory animals. It would, in fact, lack those properties by which its presence could be detected. Such a basic virus, being passed with other respiratory pathogens might, by chance passage through individuals lacking A antibody or otherwise having low powers of resistance, increase in virulence and power to form A antigen. Andrewes pictures influenza virus as increasing in this way through varying grades of virulence. Grade II virus is the hypothetical agent responsible for the clinical influenza at present called Y. When Grade IV has been reached, the virus would be infective for ferrets, sometimes for mice and would now be recognizable as A. When the highest grades of virulence (Grades VI and VII) were attained, influenza in man would occur in pandemic form. The occurrence of influenza in a community may also, of course, be influenced by specific or non-specific resistance to the virus; nor need the viruses of one outbreak all belong to the same grade of virulence.

Epidemiological records suggest that since the 1890 pandemic, influenza has been much more prevalent in Britain than before that event. Although influenza A has not been detected in certain years since 1933, the prevalence of clinical influenza every year has been high in comparison with that of the pre-1890 era. Andrewes suggests that the influenza virus has been regularly taking a heavier toll of human lives since 1890, but that only in certain years have circumstances allowed it to attain that grade at which it becomes recognizable as influenza A. In the field of prevention Andrewes suggests that improved aerial hygiene, such as better ventilation, the use of ultraviolet radiation, and antiseptic mists, if they decreased other respiratory infections, might make it difficult for influenza virus to acquire epidemic virulence. While present methods of vaccination have only a limited value in protecting individuals, the disease might quickly fade out if introduced into a recently vaccinated closed community with a high antibody level. While the use of intranasal instillation of attenuated virus might be an effective immunizing procedure, such a method could only be used in face of a grave menace and if one were fairly sure that the virulence of such a virus would not get beyond control.

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STUDIES ON AIR-BORNE VIRUS INFECTIONS: I. Experimental Technique and Preliminary Observations on Influenza and Infectious Ectromelia

by D. G. F. Edward, W. J. Elford & P. P. Laidlaw, *Journal of Hygiene*, **43**, 1–10, January 1943

As aerial warfare necessitated the crowding together of people in air raid shelters in the large towns of Britain, the dangers of air-borne infection in such conditions seemed an urgent problem. For this reason an experimental investigation was begun soon after the outbreak of war by a group of workers at the *National Institute for Medical Research* in London under the direction of the late Sir Patrick Laidlaw. Because epidemic influenza was one of the diseases likely to spread in shelters, experiments with the influenza virus were made. Wells & Brown (1936) in America had previously shown that influenza A virus could be recovered from the air in a tank up to one hour after suspension of virus had been atomized into it, and more recently Wells & Henle (1941) have recorded the transmission of influenza infection to mice by exposing them to aerosols of the virus.

The virus used by Laidlaw and his colleagues was the mouse-adapted strain of P.R. 8 influenza A virus. The virus suspension was obtained from the lungs of infected mice. It was atomized into a small flask where the larger droplets were trapped on the bottom of the flask. The aerosol was then passed into a large aspirator jar over water or a saturated solution of calcium chloride. The aerosol in the aspirator jar was usually allowed to stand for about 15 minutes to allow the larger particles to settle. It was then passed to a desiccator containing mice which were exposed to the aerosol for periods of up to 30 minutes. Samples of the aerosol could also be trapped in a separate small centrifuge bottle containing a measured amount of broth. The virus content in the aerosol could then be estimated by tests of this broth for infectivity in mice by nasal instillation.

The length of time during which the aerosols retained their infectivity was investigated. The aerosols were sampled immediately and at chosen intervals after atomization (*a*) by filling the centrifuge bottles and then titrating the virus deposited in the broth by centrifugation, and (*b*) by direct exposure of mice in the desiccator. When an aerosol was collected over water it was found that the loss in infectivity was slight after 15 minutes, but after 30 minutes the loss amounted to 90 % and after 1 hour to 99 %. On the other hand, the dry aerosol (collected over saturated solution of calcium chloride) was much more persistent. After 1 hour there had been a tenfold decrease in infectivity and after 3 hours 1 % of virus remained. Further experiments appeared to show that the more rapid disappearance of infected particles in an atmosphere of high humidity was due to settling out. It was estimated that the aerosol collected over water had a mean particle size of approximately 2·3 μ while that over saturated calcium chloride solution was 1·3 μ.

To estimate the concentration of virus in the aerosols, mice were exposed either for a fixed time to dilutions of aerosol or for varying times to full strength aerosol. It appeared that 500 cm.^{3} of tenfold diluted aerosol breathed by a mouse would produce an influenzal infection comparable to that resulting when the equivalent of 5 cm.^{3} of full strength aerosol was given in fluid intranasally. The authors suggest that, of breathed virus, as little as 1 % may reach the lungs, most of the virus being retained in the nasal and respiratory passages.

The methods described have been found by the authors to be suitable for the study of other viruses—infectious ectromelia of mice, vaccinia and herpes—and are particularly valuable for the study of the disinfectant action of ultra-violet rays and chemical antiseptic aerosols on virus suspended in the air.

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STUDIES ON AIR-BORNE VIRUS INFECTIONS: II. The Killing of Virus Aerosols by Ultra-Violet Radiation.

by D. G. F. Edward, D. Lush & R. B. Bourdillon, *Journal of Hygiene*, **43**, 11–15, January 1943

The effectiveness of ultra-violet rays in destroying sprays of bacterial cultures has been demonstrated by Wells & Wells (1936) and confirmed by others (Andrewes *et al.*, 1940). Wells & Brown (1936) and Wells & Henle (1940) have shown that aerosols of influenza virus could be rendered non-infective for ferrets and mice by ultra-violet rays. The present authors, working at the *National Institute for Medical Research* in London, have now investigated the effect of ultra-violet rays on the viruses of influenza A, vaccinia, and herpes simplex under laboratory conditions.

Suspensions of influenza virus were prepared from infected mouse lungs. Infected chorioallantoic membranes from hens' eggs were used as the source of virus for vaccinia and herpes. The technique used to obtain the aerosol sprays was that described by Edward, Elford & Laidlaw [*see BMB* **66**], the aerosols being collected over calcium chloride solution. Two low pressure mercury vapour "germicidal" lamps were used as sources of ultra-violet radiation; both gave a high proportion of their radiation at wave-length 2537A. The virus aerosols were exposed at a distance of approximately 2 cm. to the light while passing through either (1) an annular silica cylinder of mean radius 3·08 cm. or (2) a silica tube closely twisted into a spiral of 4·75 cm. mean radius.

The presence of influenza virus in irradiated aerosols was

tested by exposing mice to them. Tests for the presence of vaccinia or herpes virus were made by passing the aerosols into centrifuge bottles containing a measured amount of broth. After centrifugation the broth was tested for infectivity on the chorioallantoic membranes of hens' eggs. It was found that radiation was effective in killing aerosols of influenza virus exposed for six seconds or more. No viable virus was recovered from 15 cm.^{3} of vaccinia aerosol irradiated for 1 second whereas there were from 175 to 600 virus particles in the same volume of unirradiated aerosol. Probably more than 90% of the virus was killed when the exposure time was reduced to 0·5 second. The findings with herpes aerosols were similar to those obtained with vaccinia virus.

The results confirm the susceptibility of influenza virus to ultra-violet rays as demonstrated by Wells and his colleagues; they further support the view that "germicidal" lamps are likely to be useful in reducing the infectivity of air contaminated with particles from persons suffering from virus infections of the respiratory tract.

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LABORATORY INFECTION WITH MURINE TYPHUS

by M. van den Ende, E. H. R. Harries, C. H. Stuart-Harris & A. J. Steigman, *Lancet*, **1**, 328–332, 13/3/43

This paper describes the occurrence of typhus infection in five workers in a research laboratory in London and seven workers in a military laboratory in another part of England. The account is written by the staff of two laboratories and *London County Council* medical officers who had charge of certain of the cases. Four of the London workers, who had received a course of Castañeda rat-lung vaccine and two courses of Cox's yolk-sac vaccine, all became ill 2–10 days after commencing work involving the intranasal inoculation in mice of rickettsiæ of murine typhus. Another worker who had received one course of each type of vaccine was infected and developed symptoms later. The workers in the military laboratory had received a course of Cox's vaccine and a "recall" dose some months later. Very shortly afterwards intranasal mouse inoculations and egg culture of the murine virus were begun, and five out of the seven workers exposed to the greatest risk developed typhus. Two others, including one who paid only short daily visits to the laboratory without actually taking part in the work, became infected later. At the second laboratory a Tunisian epidemic strain was also being used, but the clinical and other findings in the cases were the same as those in the London laboratory.

Gloves, masks, glass and metal inoculation boxes and, at one laboratory, oilskin capes were used during the intranasal inoculation of the mice, but from trials made with *Chromobacterium prodigiosum* it is clear that large numbers of infective particles are disseminated and remain in the air for the greater part of an hour after such work. The authors speculate as to whether the inhalation of infective louse fæces may play a part in the natural spread of typhus.

The clinical details of the cases, of which three were moderately severe, five mild, and four ambulant, are given. Onset was indefinite but headaches were constant and muscular pains were a frequent symptom. Ten to 14 days of remittent or intermittent fever followed, with chills and progressive worsening of the symptoms as evening approached. In only three of the cases was there a definite rash. One had severe sequelæ, mainly tachycardia, indicating the need for prolonged convalescence with absolute rest.

The virus was not recovered from any patient by animal inoculation of the blood, or by the feeding of lice in the one case in which it was tried. The fact that all the subjects had had courses of vaccine may account for this failure, and for the mildness of the disease even in the three subjects over 45 years of age. All patients, in the second week, developed or showed an increase in titre of agglutinins to Proteus OX19, attaining a maximum in early convalescence. The only significant change in the blood picture was a neutropenia with a relative or absolute monocytosis in all but one of the 8 cases examined. The neutrophil count averaged 3776, monocytes 702. There was a relative monocytosis of 5–18% (normal, 2–5%). The blood picture returned to normal after 2 or 3 weeks. Since the symptoms in the first week are indefinite, and the Weil-Felix reaction is not yet helpful, these findings may be of value, as the only other infections in which they occur are rubella and infectious mononucleosis, which are unlikely to be mistaken for typhus.

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EXPERIENCES WITH TYPING OF TYPHOID BACILLI BY MEANS OF Vi BACTERIOPHAGE : A Report to the Medical Research Council

by A. Felix, *British Medical Journal*, **1**, 435–438, 10/4/43

The author, whose laboratory researches on typhus and typhoid fever are well known, first described the "Vi" or virulence antigen which exists in most freshly isolated strains of *Bact. typhosum*. Craigie & Yen (1938), working in Canada, were able to obtain preparations of bacteriophage which were specific in their action against certain strains of typhoid bacilli possessing the Vi antigen, and could be used for identifying these strains. All strains isolated from persons infected from the same source are of the same phage-type. The phage-type of any strain is a stable character, so that cultures isolated over a period of time from a single carrier are constantly found to be of the same type. Craigie found that he could type almost all his typhoid strains by the use of 18 phages. It was clear, therefore, that this new method provided the epidemiologist with a valuable means of proving the common origin of a group of cases and perhaps of detecting the source of infection.

Felix is at present working with the *Emergency Public Health Laboratory Service*, which has been organised during the war by the *Medical Research Council* [*see BMB* 64], and through this Service he collected and typed 440 strains of typhoid bacilli isolated in Great Britain during 1940–42. Although the cases and carriers thus typed form only a fraction of the total number of cases notified, they give some estimate of the phage types prevalent during that period.

Of the 440 strains, 314 were typed by nine of Craigie's phages. Of the remaining 126, 8 strains did not possess Vi antigen and 118 were "imperfect" Vi forms, that is, they contained Vi antigen but were resistant to the action of the 18 specific phages. Using the method described by the original workers, the present author was able to prepare four new Vi-type phages by means of which 49 of the "imperfect" forms could be grouped. It was thus possible to type all but 15·9% of the typhoid strains. Half of these untyped strains were derived from three outbreaks. The commonest types were E1, A and C. There was evidence that 11 of the 13 types found were indigenous to Great Britain, the other 2 representing infections probably acquired in other parts of the world.

Endemic foci of infection, maintained by chronic carriers, still exist throughout the country. The number and importance of these foci can be judged by the experience in one English county, where 62 cases of typhoid occurred in the period under review. The phage test showed that these cases originated from at least six different sources and their distribution made it likely that the number of active foci was considerably greater. It is obvious that the investigation of sporadic cases is almost impossible without some means of separating infections arising from different sources from one another. The phage test is at present the only laboratory method which enables this to be done, and the present paper is a plea for the extended use of the typing technique.

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AN ENDEMIOLOGICAL STUDY OF *BACT. TYPHOSUM* TYPE D4

by W. H. Bradley, *British Medical Journal*, **1**, 435–441, 10/4/43

The author is an epidemiologist on the staff of the British Ministry of Health. This paper gives an interesting account

of the way in which the co-ordinated efforts of the medical officers in the field and the workers in the laboratory were successful in tracing the vehicle and source of infection of 23 cases of typhoid fever which occurred over a period of two years in three counties not far from London.

The first cases occurred in the early months of 1941. They appeared in different households scattered over an area of about 100 square miles [259 km^2.] and there was no obvious connection between them. Such cases present great difficulty to the epidemiologist who, until recently, had no means of knowing whether they were infected from one or from a number of different sources. The method of typing typhoid bacilli by the bacteriophage test [*see BMB* 69] is, however, now available. The organisms from all these cases were found to belong to a new type, designated D4, which had not hitherto been described. This was of considerable significance since it suggested at once that all the victims had been infected from a single source.

The problem was not solved until the following year. More cases appeared in another town in the same area, and secondary cases occurred in other districts. The connection of these cases with the same source of infection was strongly suggested by the fact that the organism isolated was again *Bact. typhosum* D4, a type not reported from any other part of the country.

It was suspected that infection might have been conveyed by milk, but the affected persons had been supplied by at least nine different dealers. It was found that these suppliers all obtained their milk from one distributing depot, which in turn received milk from four sources. By careful observation of the method of distribution, one of these sources, consisting of a group of 13 farms, became suspect. The particular farm was fortunately indicated by the occurrence of typhoid fever in a labourer who had worked there, and further investigation revealed that the farmer was the carrier of type D4 typhoid bacilli responsible for the widespread infections. He lived 100 miles distant from the scene of most of these infections. It was probable that the milk had become infected not during milking but by rinsing of churns with contaminated water from the well on the farm. Contamination of the milk on four days only during the two years could have accounted for the occurrence of all the cases.

Apart from the assistance given to the investigator by the new typing technique, this account is of interest in that it shows that a milk-borne outbreak is not necessarily explosive and of great magnitude, but may take the form of scattered sporadic cases.

[*Reference is also made to this outbreak in BMB* 64.]

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OBSERVATIONS ON FLEXNER DYSENTERY

by W. A. Caldwell & S. W. Hardwick, *Edinburgh Medical Journal*, **50**, 129–139, March 1943

The authors, of the Mental Health Services of the *London County Council*, report an epidemic of dysentery involving 102 male and 255 female cases which occurred in *West Park* Hospital, Surrey, in 1941 and the early months of 1942. During the first nine months of the outbreak, MacConkey's medium was used for making cultures from the stools, and with this medium only a small number of female cases proved positive to *B. dysenteriæ Flexner*. In November, 1941, the desoxycholate citrate medium described by Hynes (1942) was substituted, and stools were collected in a special glycerine saline solution containing phenol red made to a pH of 7·4 with sodium phosphate. In this solution there is no urgency for stools to be cultured. Rectal swabbing, which had been carried out extensively, was discontinued, as it had been found that fæces gave a higher percentage of positive results. By these new measures it was demonstrated that 70 % of female cases were of true Flexner dysentery.

Early cases were treated by the sodium sulphate treatment of Manson-Bahr (1939), but when sulphaguanidine became available this was substituted, the course of treatment given being that described by Anderson & Cruickshank (1941) with the dosage increased slightly. Results from this sulphonamide were highly satisfactory. When given within three days of the onset of symptoms, stools became bacteriologically negative within seven days and symptoms ceased within two or three days. If treatment was delayed for seven days or more, symptoms persisted longer and stools remained positive up to 25 days after the first administration of the sulphaguanidine. Firor (1942) recommends succinyl sulphathiazole in preference to sulphaguanidine, as it is of high anti-bacterial potency, low toxicity, is absorbed poorly, and has a high local concentration in the bowel. The present authors intend to treat in the near future a few sulphaguanidine-resistant cases and three chronic carriers (one of over two years' duration) with this new drug.

A detailed investigation of the disease in a particular section of the hospital revealed the interesting fact that 20 % of patients had bacteriologically positive stools without symptoms of any kind, even after close interrogation and observation. These cases were occurring *pari passu* with overt cases of the disease. It was found that in the average case of clinical dysentery, without treatment, the organism continued to be excreted for an average of 32 days after the onset of the disease, whilst the bacillus was excreted for only half that period in symptomless cases.

Following this finding, and in view of the lessons exemplified in the observations of McMillan, Hunter & Rhodes (1940), stricter vigilance was kept over staff nursing in wards where dysentery cases arose. In the female dysentery ward, where there were fourteen nurses, nine were found on close questioning to have had attacks suggestive of mild dysentery, and another nurse had positive stools with a complete absence of symptoms. There is reason to believe that non-resident staff go sick with dysentery which is unrecognised by their doctors, as several have proved to have positive stools on return to work after an illness suggestive of alimentary disturbance.

At the beginning of the epidemic the prophylactic dysenteric vaccine recommended by Paddle (1938) was given to some 1,600 patients. Although the vaccine was prepared in the same laboratory and with the same technique as Paddle's the results obtained were disappointing. From agglutination tests carried out in the present series it appears that any immunity conferred is of short duration, probably not longer than four weeks. However, the vaccine has proved of value in wards where one or two sporadic cases occurred. It must be given to every patient in the ward as soon as an active case is discovered and doses of 0·5 cm.^{3} and 1·0 cm.^{3} of vaccine containing 10^9 organisms per cubic centimetre are recommended.

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HOSPITAL DIARRHŒA

by P. Evans, *Archives of Disease in Childhood*, **17**, 130–135, September 1942

Although institutional diseases have declined in importance, hospital diarrhœa still kills a large number of infants. The author, who is Assistant Physician to the Children's Department of *King's College* Hospital, London, discusses 203 cases of diarrhœa which occurred after admission to one of the Emergency Hospitals organised during the war by the Ministry of Health. An attempt is made in this paper to classify the attacks epidemiologically as a guide to prophylaxis.

There were 110–130 beds available for children, arranged in five nursing units. In 27 months nearly 2000 children were admitted, of which nearly 500 were infants under 2 years. In the 203 attacks of diarrhœa the total attack rate was 11 per 100 admissions. In older children the attack rate was 8, and in infants 20, per 100 admissions. No seasonal incidence was apparent. There were 190 epidemic and 13 sporadic attacks. The author divides the epidemics into food poisoning, bacillary dysentery, and other outbreaks. The latter, and the sporadic cases, were almost confined to infants under 2 years.

Two outbreaks of food poisoning were traced to the consumption of meat minced in an imperfectly cleaned mincer. Forty-nine children were affected, whereas meat from the same source, but unminced, was innocuous. Chemical changes could have been produced in a pabulum of meat remaining in the mincer from the previous day by the activity of ordinarily non-pathogenic organisms (Topley & Wilson, 1936) and in these circumstances the toxins would be mixed with part of the next day's mince.

Bacillary dysentery was caused by *Bact. Sonnei*. Five outbreaks occurred, affecting 10 nurses and 89 children. On two occasions the epidemics affected over 49 people before coming under control. The reasons for this failure to prevent an obviously preventable disease were:

1. Difficulties of early diagnosis and failure to isolate early. Confusion with surgical conditions which cause abdominal pain, pyrexia and vomiting.
2. The disease is mild, especially in nurses, and may escape detection. Convalescent and healthy temporary carriers occur.
3. Nursing difficulties with incontinent children, and the difficulty of obtaining nurses in wartime who are entirely adequate in training and numbers.
4. Dysentery in England is usually mild and there may be a failure of nursing and medical staff to regard the disease seriously, although it can be fatal in infants (Nabarro & Signy, 1932). Failure among pædiatricians to insist on the same evidence of freedom from infection as is required in typhoid fever.
5. Slowness among bacteriologists in using improved methods of detection.

The other outbreaks of diarrhœa affecting mainly infants were due to parenteral infections, which caused simultaneous respiratory infections in older children in the same wards.

The smallest group, the sporadic cases, produced the most severe symptoms. Of 6 children more than 1 year old all survived, but of 7 younger than 1 year, 6 died. Dehydration was marked in all cases, a parenteral infection was often present, and the children were underweight.

The author suggests that prophylaxis should be worked out independently for each hospital, with special reference to sterilisation of feeds and bottles, disposal of excreta, improved bacteriological methods, health of nurses, alertness of doctors, isolation, air-sterilisation and use of masks, and prompt diagnosis of urinary infection in children.

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THE INFLUENCE OF SOCIAL CONDITIONS UPON DIPHTHERIA, MEASLES, TUBERCULOSIS AND WHOOPING COUGH IN EARLY CHILDHOOD IN LONDON

by G. P. Wright & H. P. Wright, *Journal of Hygiene*, 42, 451–473, October 1942

The periodic national census records collected by the Registrar General and the "*New Survey of London Life and Labour*" produced by the London School of Economics, together provide very detailed information about the social conditions of the people living in the Administrative County of London. With the help of this unusually extensive collection of data, the authors, working in the Department of Pathology at *Guy's Hospital*, have examined the effects of certain social factors upon the mortalities and morbidities of some of the commoner specific infectious diseases of children below the age of five years. They have done this chiefly by correlating the medical and social data for the twenty-eight Metropolitan Boroughs into which London is subdivided for purposes of local administration. The boroughs vary considerably in their wealth or poverty, and thus provide a valuable source of material for such a statistical analysis.

The mortalities of young children from measles and whooping cough were particularly high in those boroughs in which overcrowding, but not necessarily poverty, was most prevalent. On the other hand, the mortalities from diphtheria and tuberculosis tended to be rather less dependent upon the quality of the local housing conditions, and to be greatest in districts in which a high proportion of the population followed unskilled and relatively poorly-paid occupations, or lived below the "poverty line." Measles and whooping cough thus appeared to be diseases specifically resulting from overcrowding, while diphtheria and tuberculosis were diseases to whose causes poverty contributed in a greater variety of ways. The prevalence of diphtheria, alone of the four diseases, was dependent upon the number of children of school-age and under who were living in the family.

The morbidity statistics are less complete and, in consequence of the occurrence of sub-clinical cases, inevitably less reliable than those for mortalities, but they bore out the same general conclusions. They also provided an explanation for the very strong correlation that was found between overcrowding and the high mortalities from measles and whooping cough. In badly housed districts the infants tend to acquire infection with these diseases at an exceptionally early age, and since the case-fatality rates decline particularly rapidly with increasing age, the elevated morbidities amongst the youngest of the infants, which result from overcrowding, are necessarily reflected in exceptionally high local mortalities. The findings in this study emphasize very strongly, therefore, the great desirability of taking every public health precaution likely to postpone the age at which a child contracts these two serious infectious diseases.

Since scarcely any unpasteurised milk is now consumed in London, open cases of tuberculosis amongst adults provide almost the sole source of tuberculosis infection for young children. This is shown by the strong correlation found between the mortality from tuberculosis of young children and that for adults of 25 to 44 years old, whose age group includes much the largest proportion of the parents of young families. Of significance, too, is the finding that the correlation between the tuberculosis mortalities of infants and adults is higher for male adults (the "fathers") than for female (the "mothers"), a conclusion that has also been reached after several recent field studies in London and various European cities. The closer association of this disease in infancy with poor economic resources than with poor housing accommodation, indicates that important factors in addition to that of overcrowding influence the prevalence of tuberculosis amongst young children. It is not yet possible, however, to go further than to suspect that nutrition is one of the most, if not the most, significant of these other factors.

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RECENT TRENDS OF SOME INFECTIOUS DISEASES

by W. J. Martin, *British Medical Journal*, 2, 540–542, 7/11/42

The author, who is a member of the statistical staff of the *Medical Research Council*, attempts an estimate of the number of lives saved by new methods of treatment in some infectious diseases. Chief among these methods has been the use of the sulphonamides. This survey in most cases covers the last decade and is based on the ratio of deaths to notifications, since the population at risk is not definitely known for 1940 and 1941.

Cerebrospinal Fever. In England and Wales the average number of deaths per 100 notifications during 1934 to 1937 was 67. On this basis the expected number of deaths for 1939 to 1941 would have been 16,876. Actually, 5,264 deaths were registered. Again taking the figures of the last war for comparison, 8,068 cases were registered during the epidemic of 1915 to 1917, with a fatality rate of 64%. The reasonable supposition is that the introduction of sulphapyridine has saved about 10,000 lives from this disease during 1939 to 1941 and reduced the fatality rate to one-third its former figure.

Pneumonia. The position is complicated by the large annual fluctuations in the mortality rate. Accordingly, the author uses the incidence of bronchitis as an index of the favourability or otherwise of the various years. On this basis an undoubted decrease in the mortality rate for pneumonia can be shown. Estimation of its extent, however, remains speculative. Nevertheless it does seem that the introduction of sulphapyridine has resulted in a reduction of mortality of 10% during the years 1939 to 1941. This represents a saving of 7,500 lives during that period. In Scotland the figures for lobar pneumonia are differentiated from those for other forms of pneumonia. There is again a substantial reduction in the mortality, and this is seen to be

due chiefly to an improvement in the figures for lobar pneumonia. The deaths from lobar pneumonia were reduced by 39 % below the average rate before 1939, while in the other forms of pneumonia there was little change.

Puerperal Sepsis. In the 10 years before the present war, the disease accounted for 40 % of the total maternal mortality. There was an average of approximately 17 deaths per 10,000 live births. During 1939 there was a striking reduction in deaths from this cause, and this improvement was maintained during 1940 and 1941. The average for these 3 years was 9 per 10,000 live births from puerperal sepsis, the improvement again being due to the use of the sulphonamide group of drugs.

Measles. No striking and sudden drop in the mortality can be demonstrated as in the case of the diseases already mentioned. There has been, however, a steady improvement over the past 20 years, due to a combination of factors. These include serum prophylaxis, improved nutrition, better standards of living, earlier and more frequent admissions to hospital and oxygen therapy. The virulence of the organisms may be lower and it is impossible to assess the relative importance of these different factors, but together they have resulted in a reduction of the mortality in childhood of about three-quarters of what it was 20 years ago. This represents a saving of about 6,500 lives during 1940 and 1941.

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A CLINICAL AND BACTERIOLOGICAL SURVEY OF PNEUMONIA IN CHILDHOOD

by E. Hendry, *Archives of Disease in Childhood*, **17**, 111–121, September 1942

This study from the Department of Pediatrics, Glasgow University, is based on 186 consecutive cases of pneumonia admitted to the Royal Hospital for Sick Children, Glasgow, between October 1st, 1939, and September 30th, 1940. Of these, 182 suffered from primary and 4 from secondary pneumonia.

The bacteriological investigation was made on:

(1) Throat swabs and nasal swabs from all patients on admission, at intervals during their stay in hospital, and after discharge.
(2) Pus from middle ear and pleural cavities when these regions were involved.
(3) Cultures from lung and splenic tissue, and from bile, in fatal cases.
(4) Cerebro-spinal fluid in three cases.

The causal organism was identified by intraperitoneal injection of broth cultures of the above material into mice. The resulting peritoneal exudate, or occasionally culture from the heart blood of the mouse, was used for typing the pneumococcus against Lederle's series of immune rabbit sera (Neufeld reaction).

In 57 % of the 186 cases, a pneumococcus was cultured from the throat or elsewhere. From the remainder streptococci, staphylococci, coliform bacilli or a mixture of these were the only organisms found on repeated examination. These cases could thus be divided into two groups: (1) those infected with the pneumococcus and (2) those infected with other organisms.

Clinical Summary

The greatest number of cases per month occurred in January, May, and August in that order. The unexpected rises in incidence in May and August were caused mainly by infection with type 19 pneumococcus. This organism accounted for 20·8 % of all cases, considering the year as a whole. Of the children suffering from pneumococcal pneumonia 60·3 %, and of those with non-pneumococcal pneumonia 73·7 %, were under 2 years of age. Bad housing conditions seemed to predispose to pneumococcal infection, though no one type of pneumococcus was particularly responsible.

The disease usually ran a mild to moderately severe course for both groups of patients. Sulphapyridine was given routinely to all and was necessary, on an average, for 8·75 days for each patient in the pneumococcal and for 7·6 days for each patient in the non-pneumococcal group. The leucocyte counts were surprisingly low (on admission to hospital and before the treatment with sulphapyridine began) and there was no evidence that one type of pneumococcus produced a particular leucocyte response.

An uncomplicated recovery took place in 85 % of the pneumococcal and in 90 % of the non-pneumococcal group.

Complications

In both groups otitis media was the complication most frequently encountered and it occurred in seven pneumococcal cases. The types of pneumococcus found in these cases were 6, 22, 23 (two cases), 24, and 29 and in one case there was a mixed infection with types 20 and 31. All cases were fatal, as were two of the eight occurring in the non-pneumococcal group.

Three cases, all fatal, developed meningitis (types 6, 19, and 25). From the first two, the pneumococcus was isolated from the throat swab and cerebrospinal fluid during life, and from the third from the cerebrospinal fluid only during life and from splenic and lung tissue at *post-mortem* examination.

Arthritis occurred in one case in which culture from a throat swab and from joint fluid yielded type 23 pneumococcus.

In the only case developing peritonitis it was impossible to determine the type of infecting organism as *post-mortem* examination was refused. Pneumococci, types 3 and 14, were isolated repeatedly from throat swabs during life in this case.

Mortality

The total death rate was 13·5 %. In cases under two years of age in the pneumococcal group the mortality was 23 %, while it was only 5 % in cases over 2 years of age in this group. In the non-pneumococcal group the mortality was 14 % under 2 years of age and nil over two years of age. For both groups the mortalities were 19 % under and 3 % over two years of age.

Pneumonia caused by any of the pneumococci was therefore more serious than that caused by other organisms, but sulphapyridine was equally effective in both groups.

Recovery was complete in all uncomplicated cases but was slow in three cases (types 1, 6, and 22). The pneumococcus usually disappeared from the patient's throat soon after the acute stage of the illness was over.

Bacteriological Summary

Types 6 (18·5 %) and 19 (20·8 %) were the pneumococci most often isolated, followed by types 1, 9, 11, 22, 23, and 29 in this order. Types 28, 32, and 33 were not found.

Type 1 infection occurred more frequently in children over than under two years of age, but the only type 2 pneumococcus cultured was isolated from the throat of a child aged fourteen weeks.

Discussion

Pneumonia in childhood may be caused by almost any of the known types of pneumococci, against all of which sulphapyridine seems equally effective. All types, except 28 and 32, were shown to have been responsible for the disease. Type 33 was not tested for, as the appropriate specific immune serum was not available.

In the majority of cases the course of the disease was remarkably similar. No evidence could be obtained to show that a particular type of illness with distinctive signs and symptoms was caused by any one pneumococcus.

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AN IMPROVED UNHEATED BLOOD TELLURITE MEDIUM FOR THE DIAGNOSIS OF *C. DIPHTHERIÆ*

by K. I. Johnstone & K. Zinnemann, *Journal of Pathology and Bacteriology*, **55**, 53–61, January 1943

The tellurite medium containing heated blood on which McLeod and his colleagues of Leeds (Anderson, Happold, McLeod & Thomson, 1931) first described the different types of diphtheria bacilli has been found to inhibit the growth of certain *mitis* and a few *gravis* strains occurring in various parts of the world. Of the media containing unheated blood, designed to overcome this difficulty, the most recent is that of Hoyle (1941), who uses a Lab-Lemco (a meat

extract) base and blood laked by freezing and thawing, by distilled water or, more conveniently, by saponin. The aim of the present workers, also of the Department of Pathology and Bacteriology of Leeds University, was to devise a medium which was not inhibitory to any strains and which also retained the excellent type-differentiation of the original McLeod medium.

As in the medium of Gundel and Tietz, a stock tellurite-blood mixture is prepared. Two parts of sterile 1% potassium tellurite solution are added to five parts of defibrinated rabbit or horse blood. Human blood is slightly less satisfactory. After 1–3 days' incubation at 37° C. the blood will be found to be laked and the mixture can then be stored indefinitely in the cold. The best results are not obtained until it has been stored for three weeks. To prepare the medium 130 cm.^{3} of meat extract prepared by the low temperature method used for McLeod's medium are added to 130 cm.^{3} of 5% agar in water at 50° C.; 42 cm.^{3} of the well-shaken tellurite-blood mixture are added and plates are poured. The medium is of the colour of red burgundy wine, darkening to mahogany on incubation.

All strains of *C. diphtheriæ gravis, mitis* and *intermedius* grew well in 18 hours. *Gravis* colonies and those of *intermedius* type, which were black with a translucent periphery, were larger than on the previously described media. The flat rough greyish crenated colonies of the *gravis* strains and the darker smooth shiny colonies of the *mitis* strains were readily recognisable. Most colonies of other organisms were brownish-black or white, and those of nasal diphtheroids smaller and greyer than the *intermedius* strains with which they are liable to be confused. The addition of indicator dyes and of urea to the medium produced unsatisfactory results.

From the results of the inoculation of a series of swabs on both media it is clear that the new medium has the desired advantage over McLeod's medium. In respect to colony size and type-differentiation it has some advantage over Hoyle's medium, but this was found to be largely due to the use of the low temperature meat extract. This extract is never heated above 75° C. and is sterilised by filtration. When Hoyle's medium was made up with this extract the advantage of the new medium disappeared to a great extent. When 1407 routine swabs were inoculated, first on inspissated serum and then on the new medium, the former detected 85·4% and the latter 98% of the total number of positive swabs. It is thus likely that if the new medium alone had been used very few positives would have been missed.

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THE NATURE OF THE RHEUMATIC CHILD

by D. Hubble, *British Medical Journal*, **1**, 121–125 & 154–158, 30/1/43 & 6/2/43

In spite of intensive research the problem of the ætiology of the rheumatic state in childhood is still unsolved. This is a reason for returning to the study of the disposition of the rheumatic child. The purpose of this paper is to answer the question "Why did this child become rheumatic, and how can the ætiological factors be controlled?"

Growing Pains. It was thought from the beginning of the century until after the last war that growing pains were a sign of early rheumatic taint. Doubt was cast on this by Winnicott (1931), Sheldon (1936), and Hawksley (1939), and Kaiser found limb pains in 7% of 48,000 normal children in 1927. In 1936 the incidence of cardiac rheumatism was only 0·8% in over 300,000 London children examined.

The causation of growing pains has been attributed to fatigue, normal growth, latent infection, postural deformities, and fibrositis. Winnicott ascribes it to an emotional disorder associated with the child's growth. Indeed there is a response to simple psychotherapeutic and sedative measures. The children are sulky, irritable, fatigued, sleepless, and cry incessantly. The pains are in the muscles of the thigh, and come on at the end of the day or during the night. The pains of subacute rheumatism, however, are in the joints, are present in the morning and persist all day, and are worsened by walking. Sheldon (1936) found that only 2 out of 189 children with growing pains developed rheumatism after an interval of 4 years.

The author concludes that growing pains in children reflect a disorder of psychological adjustment and that they are quickly removed by simple and appropriate treatment. Active rheumatism should never be diagnosed unless arthritis or carditis is present. The possibility that subacute rheumatism represents the growing pains of children predisposed to rheumatism cannot be denied. This consideration is only of theoretical importance in ætiology, and is of no account in the treatment of growing pains.

Chorea. Chorea is usually regarded as a brain inflammation caused by the rheumatic invader, but its structural pathology is unknown. Buzzard & Greenfield (1921) and others define chorea as a functional disorder of the nervous system characterised by sudden aimless irregular movements, muscular weakness, and emotional instability.

Clinically there is no evidence of inflammation and no fever, leucocytosis, or changes in the cerebrospinal fluid. The movements cease during sleep. Findlay (1931), Coombs (1924) and others believe chorea to be emotionally induced, usually by the stresses of education, sudden frights, domestic unhappiness, etc. It is commoner in girls, whose nervous system is less stable.

Chorea is a frequent associate of the rheumatic state, and it is evident that the effects of rheumatic inflammation on the cerebrum of a predisposed child are the same as those of prolonged emotional strain. This association can be reconciled if the rheumatic state is regarded as having 2 components: nervous instability, and inflammation of the heart and joints. Both may occur independently, but either favours the development of the other.

The author concludes that chorea may be defined as a functional disorder of the nervous system, characterized by irregular motor activity and emotional instability, which develops in predisposed individuals, particularly girls of the poorer classes, following acute psychic trauma or prolonged psychic stress, or during and after the development of the rheumatic state.

Ætiological Factors in the Rheumatic State. Three factors are universally accepted. Age, social grouping, and the hæmolytic streptococcus. The age group 3 to 15 is the danger period—the age period of mental integration and adjustment from the cot to the family, and out into the world. Still (1927), and later Glover (1930), found the disease 20 to 30 times commoner in the poor than in the rich. It occurs not in the very poor, however, but in the better-class poor families. They have been in more fortunate circumstances, and have fallen on evil days. In these children the nervous strain of poverty will be greater. The factors of poor clothing, damp, malnutrition, overcrowding, etc., undoubtedly explain the association of rheumatism with poverty at all levels, although large-scale investigations in Britain by the *Medical Research Council* (1927) have established that the incidence of rheumatism is not in direct relation to the degree of poverty. The infective factor, in the form of the hæmolytic streptococcus, may find the child's resistance weakened by emotional disorder, as in the subacute rheumatic state or chorea. In the absence of nervous instability the infecting organisms may be in sufficient strength to overwhelm the body defences, *e.g.* following acute tonsillitis.

The author concludes that the almost absolute limitation of the rheumatic state to an age group and its common association with poverty do not refute the theory that nervous instability in the child is part of the rheumatic diathesis, nor does the recognised association with infection in some of its phases controvert such a theory.

Type of Child. About one-third of cases of rheumatic carditis show evidence of preceding nervous instability. The children are not neurotic but show a quantitative increase in emotion and kinesis. This nervous instability is an important factor in the development of the rheumatic state.

Treatment. The author makes the following recommendations: (1) Do not regard the child as suffering from the

rheumatic state until carditis is definitely diagnosed. This will prevent the formation of cardiac neurosis. (2) Seek for evidence of nervous instability. Treatment of this will limit the extent of the rheumatic disorder in childhood. Psychiatric treatment should be by reassurance, smoothing out of gross environmental stress, and sedation with phenobarbitone during growing pains, subacute rheumatic state, chorea, and acute rheumatism.

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TREATMENT OF SCABIES BY T.E.T.M.S.

by T. M. Clayton, *British Medical Journal*, **1**, 443–445, 10/4/43

Gordon & Seaton (1942), using weak solutions of tetraethylthiuram monosulphide (T.E.T.M.S.) on rats infected with itch-mites of the genus Notoëdres found it more lethal to the parasite than either benzyl benzoate or dimethylthianthrene. Percival (1942) cured 50 cases of human scabies with a 5 % solution but found it much less satisfactory in 0·25 % strength. The investigation reported in the present paper was undertaken by a Medical Officer of Health at a -Aid Post in Blaydon, England, to test the potency of .E.T.M.S. against the parasite responsible for scabies in uman subjects. The full strength—an emulsion containing T.E.T.M.S. 25 %; polyglycerol ricinoleate, 10 %; industrial methylated spirit, 65 %—was first tested on the arms of 15 volunteers for 3 consecutive days without dermatitis or other detriment. A preliminary routine preparation of the skin with soap and water was used on the volunteers and in subsequent cases.

After a further preliminary trial [in which 4 patients with scabietic lesions of comparative equality on both arms were selected, the one arm being treated with 25 % T.E.T.M.S. and the other with a standard solution (Ministry of Health, 1940) of benzyl benzoate], the 25 % emulsion was used on 14 severe or severely complicated cases of scabies. The entire body, except head and neck, was subjected to a uniform method of preparation with soap and water while coarse sponges were used for frictional purposes. After drying with a towel, the body was rubbed all over with the emulsion and raw or grossly septic areas were dressed with white lint wrung out of the solution. Further treatments were given at intervals of 3 and 4 days.

A second series of 93 cases were treated in a similar manner, every day or every second day, with a 5 % aqueous preparation of the 25 % emulsion and no directions were given regarding the sterilisation of bedding and clothing. Subjects in this series were visited on two subsequent dates, the first not under two to three weeks and the second not under one month after the last application of T.E.T.M.S.

Summary of Results

An approximate average number of three applications was used in each series. In the first series 11 out of 14 cases were cured, the remaining 3 being probable reinfections. In 15 volunteers and 18 patients the emulsion failed to produce a dermatitis.

It appeared to have very beneficial results upon some of the secondary concomitants of scabies.

The emulsion had a tendency to sting especially in some of the more severely affected cases, probably due to the spirit content. In the second series of 93 cases, all were cured, although a mild erythematous dermatitis was produced in 7 cases.

Comment and Suggestions

The 25 % emulsion may be found useful and time-saving in severe and hospitalised cases. Treatment, perhaps, erred on the generous side in the first series and the author suggests that a similar emulsion with a smaller percentage of T.E.T.M.S. may give comparatively good results, especially if the stinging sensation can be eliminated. [In the comparative test the 25 % T.E.T.M.S. caused a more decided retrogression of lesions than the benzyl benzoate solution (subsequently confirmed on other patients).] The preparation has proved to be a sarcopticide of potency against the human itch-mite.

In the series of cases described, and in the writer's experience generally, routine fumigation of clothing is considered unnecessary besides being expensive.

[*The extracts in square brackets relate to an experiment carried out in June* 1942, *and are included at the author's request, although no reference is made to them in the original paper.*]

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79

SPECIFIC IDENTIFICATION OF THE CHIEF PATHOGENIC CLOSTRIDIA OF GAS GANGRENE

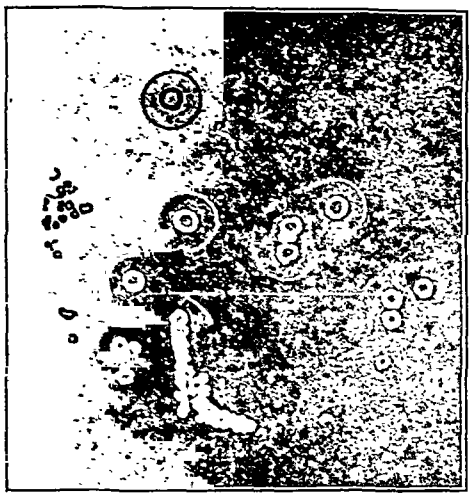
by G. F. Petrie & D. Steabben, *British Medical Journal*, **1**, 377–379, 27/3/43

The technique for isolating pathogenic anaerobes is often laborious and demands considerable skill and experience. In war-time, gas gangrene may result from infection of a severe wound with these microbes. It is, therefore, important to simplify if possible the identification of the causal anaerobes of this dangerous disease.

The authors, working in the Serum Department of the *Lister Institute of Preventive Medicine* at Elstree, England, have described a specific test for identifying with certainty—without taking into account any other differential character of the associated bacterium—the three chief pathogenic clostridia of gas gangrene, *Cl. welchii*, *Cl. septicum*, and *Cl. oedematiens*. The method consists in growing the culture on the surface of agar to which an appropriate amount of one of the specific antitoxins has been added. During the growth of the colony, toxin is produced, diffuses outwards from the colony, and interacts with the homologous anti-toxin to form a delicate but unmistakable precipitate resembling a halo round the colony. The method is identical with that used by Petrie (1932) to distinguish between rough and smooth strains of meningococcus, pneumococcus, and *B. dysenteriae* (Shiga) and also between the two main serological groups of meningococcus.

The basal medium used is a 3·5 % Evans-peptone agar to which the ingredients necessary for the production of high-grade toxin are added at the time of pouring the melted agar. Thus, for *Cl. welchii* these consist of 0·5 % glucose and 10 % of a sulphated horse-muscle extract (Macfarlane & Knight, 1941); for *Cl. oedematiens*, 10 % of the horse-muscle extract *without glucose*; and for *Cl. septicum*, 0·5 % glucose and 10 % normal horse serum. Lastly there is added 1 cm^3. of the appropriate antitoxin diluted in broth so as to give a concentration of 8 units of antitoxin per $cm.^3$ of the medium. After the melted agar has been poured into the culture dishes, they should be dried in an incubator at 37° C. for at least 5 hours to prevent motile organisms from forming a film over the surface. The cultures may be made in the usual way, or a heavy inoculation with a platinum-loopful of a pure or reasonably pure culture can be implanted on the agar at any chosen site. The growths are examined after 24 or 48 hours' incubation at 37° C. in an anaerobic jar. If the resulting colonies are well-grown but show no precipitate, they should be placed at room temperature aerobically and observed daily, because the haloes, especially those of *Cl. oedematiens*, may be slow in appearing. When the precipitate has been laid down as an apparently uniform deposit and is left aerobically at room temperature, concentric (Liesegang) rings

often appear. These are so characteristic as to leave no doubt of the specific nature of the precipitate.



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Shows ring of specific precipitate round the colonies of *Cl. welchii* on a medium containing *Cl. welchii* antitoxin. Illustrations of the rings produced with *Cl. septicum* and *Cl. oedematiens* accompany the original paper.

The haloes can be seen against a black background in good day-light but a simple magnifying glass is helpful, or a black screen with a source of bright light placed behind a central opening in it. The method has the advantage that the presence of other bacteria does not influence the formation of the precipitate so long as the toxin of the clostridium is not destroyed by metabolic products liberated by the contaminants. The authors express their confidence, based on present knowledge of the toxins of this group, that the test, when positive, is conclusive.

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EARLY DIAGNOSIS OF WOUND INFECTION WITH SPECIAL REFERENCE TO GAS-GANGRENE

by D. McClean, H. J. Rogers & B. W. Williams, *Lancet*, 1, 355–360, 20/3/43

The case-mortality from wound infections due to the gas-gangrene organisms remains obstinately in the region of 30–60%. In the early stage of infection, when the tissues are still capable of recovery, the clinical changes are so slight that even with considerable experience the surgeon can seldom form a definite opinion as to the presence of an anaerobic infection. In view of the difficulty of rapid bacteriological diagnosis it seemed worth while to explore the possibility of detecting the presence of actively proliferating pathogenic organisms at a stage when the infection cannot be recognised by clinical or ordinary bacteriological examination. The methods put forward by the authors of this paper from the *Lister Institute of Preventive Medicine*, Elstree, and *St. Thomas's Hospital*, London, depend upon the detection of enzymes produced by bacteria in the wound exudate. These enzymes are apparently produced by a large proportion of wound infecting organisms and can be detected by simple tests.

It has been known for some years that organisms of the gas-gangrene group, staphylococci, streptococci, and pneumococci, produce, in addition to their recognised toxins, substances which cause an immediate increase in the permeability of the connective tissues. Subsequent work has shown that these substances are very closely associated, if not identical, with a group of enzymes which hydrolyse the mucopolysaccharide known as hyaluronic acid, which is widely distributed in the connective tissue. It has recently been shown that the lecithinase produced by *Cl. welchii* is almost certainly identical with the α toxin and is immunologically specific.

The authors describe the results of infection experiments with *Cl. welchii*, *Cl. septicum* and *Cl. oedematiens* in groups of guinea-pigs. In infections caused by organisms which produce hyaluronidase, there is a steadily mounting titre of this enzyme in the oedema fluid and muscle extracts as the infection proceeds. It appears that the enzyme can be detected in the oedema fluid as soon as the latter is present in sufficient volume to be collected for examination, and in the muscle as soon as the earliest sign of infection appears. Lecithinase (alpha toxin) can ordinarily be detected at a similar stage in infections due to *Cl. welchii*.

A survey of representative strains indicates that a large proportion of *Cl. welchii* associated with clinical gas-gangrene produce hyaluronidase. All the strains of *Cl. septicum* examined produce this enzyme. The position of *Cl. oedematiens* is unsatisfactory; less than half the strains examined produce the enzyme and there is no evidence that this property is correlated with the incidence of gas-gangrene due to this organism. The lecithinase produced by *Cl. oedematiens* is of such low potency that it is unlikely to be of diagnostic significance in the tissue fluids.

The authors describe in detail methods for the detection of hyaluronidase and lecithinase which can be used in the field with the minimum of apparatus. Hyaluronidase can be detected and its concentration measured by tests depending upon its power to reduce the viscosity of hyaluronic acid (McClean & Hale, 1941) or by its power to destroy the capacity of a protein-hyaluronic acid complex to form a typical mucin-clot on the addition of acetic acid (McClean, 1943). Hyaluronic acid can be obtained from the "Wharton's jelly" of umbilical cord. Lecithinase can be detected and measured by its capacity to produce turbidity in emulsions of egg-yolk (van Heyningen, 1941) or by the liberation of acid-soluble phosphorus from lecithin (Macfarlane & Knight, 1941). Simple methods of diagnosing the bacterial source of the enzymes by means of specific neutralization tests with appropriate antisera are also described.

The authors suggest that these experimental results should be applied to the examination of clinical material from wounds in the hope that they may furnish useful diagnostic information at an early stage of infection, and thus assist both surgical and ancillary treatments.

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TETANUS IN THE MIDDLE EAST—EFFECTS OF ACTIVE IMMUNISATION

by J. S. K. Boyd & J. D. Maclennan, *Lancet*, 2, 745–749, 26/12/42

This report from two British Army bacteriologists records the incidence of tetanus during the first two years of war in the Middle East and attempts to assess the part played by active and passive immunisation in the prevention of this disease. Passive immunisation in the 1914–18 war reduced the incidence of tetanus to under 1 per 1000, but the present war is the first occasion on which active immunisation has been given an extensive trial in man. Active immunity in the British Army is produced by inoculation with formolised toxoid, two injections being given at intervals of 6 weeks and a third six months later. Antitoxin does not appear in the blood until after the second injection, when it rises, on an average, to about 0·1–1·0 units per cm.^{3} of serum, afterwards declining. The third injection results in a rise to from 2–10 units per cm.^{3} of serum—in some cases to higher levels. In the British Army it is the practice, in spite of this active immunisation, to give to wounded men 3,000 international units of antitetanic serum, to provide passive immunisation covering the period immediately after the receipt of a wound. In the 1939–40 campaign in France about 90% of men in the British Army were actively immunised. Eight cases of tetanus were reported amongst the evacuated troops and all of these were in uninoculated men.

Virulent tetanus bacilli were found in 9% of soil samples in the Middle East and Western Desert. Tetanus bacilli were cultivated in eighteen out of 214 cultures taken from serious wounds in hospital. The authors emphasise that

the mere presence of terminal-spored bacilli in wounds is of no significance for the diagnosis of tetanus and that the early diagnosis must be made on clinical grounds. In the period covered, 18 cases of tetanus were encountered in the Army of the Middle East, and the incidence in the British troops was 0·13 per 1000 wounded. In the South African force, however, in which active immunisation had not been carried out, the incidence was 1·6 per 1000 wounded. Of the 18 cases reported, 4 occurred in men who had been immunised with two doses of toxoid, and only 1 in a man who had received the full three doses; the other 13 were in unimmunised subjects. None of the 5 actively immunised men who developed tetanus had received the prophylactic dose of antitoxic serum prescribed as a routine measure: 2 of these men recovered and 3 died. In the 13 unimmunised patients who developed tetanus 7 recovered and 6 died.

The chief feature of this report is that in spite of evidence in support of the value of active immunisation between one-third and one-quarter of the cases occurred in immunised subjects. The limitations of the procedure demand attention. Detailed histories of these cases (which are given in full in the original paper) show two possible causes of failure: The first was that there was an insufficient response to immunisation; it is thought that this may be overcome by the third dose of toxoid, which was not formerly in use but is now always administered when possible. The second was that local conditions in the wound favoured massive and fulminating infection and the production of an amount of toxin incapable of neutralisation by the antitoxic powers of the body. It is clear that the protection afforded is limited and may be overcome by such a massive infection. The second cause may be prevented by the adequate surgical removal of dead tissue, which should be a routine measure in the prevention of all the anærobic infections (gas gangrene and tetanus). In one case the "closed plaster" technique prevented the early recognition of the presence of a mass of necrotic tissue.

The authors point out that their report is based upon findings in a country where the risk of tetanus is low. Whether active immunisation will give good protection where the risk is high, *e.g.* in France or Flanders, remains to be seen.

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FURTHER OBSERVATIONS ON ACUTE STAPHYLOCOCCAL INFECTION

by E. C. B. Butler & F. C. O. Valentine, *Lancet*, **1**, 194–197, 13/2/43

For the last four years the authors, Assistant Surgeon to, and Director of the Inoculation Department of, the *London Hospital*, have made a special study of acute illness due to staphylococcal infection. They now report in detail 34 cases and indicate the points they consider most important in prognosis and treatment.

In an earlier paper (Valentine & Butler, 1939) the authors described their methods of investigation. A blood culture in a solid medium was made every few days so that the rise or fall in the number of organisms in the patient's blood could be followed. Secondly, the antileucocidin in the patient's serum was titrated, as an investigation of the various antibodies produced in response to staphylococcal toxins had led the authors to conclude that antileucocidin was the most important in the development of resistance.

On the basis of these two investigations, and of the clinical state, the present series of cases is divided into 5 groups:

Group 1. The blood colony count was either very high (500–1000 colonies per cm.^{3}) at the beginning or rose rapidly, and the antileucocidin titre was not raised. Clinically, the cases were fulminating and all died within 11 days; in 4 out of 9 the infection started from a septic focus on the face.

Group 2. The colony count was above 30, but 3 out of 8 patients recovered. Death was due either to an increasing blood infection, as in group 1, or to secondary abscesses in vital organs, *e.g.* the lungs. As death did not occur for 3–6 weeks antibodies had time to form, and the antileucocidin titre was higher than in group 1.

Group 3. The colony count was below 20 and only 3 cases died out of 12. Many cases of osteomyelitis fell into this group. The antileucocidin titre rose to a high level during the illness.

Group 4. The blood culture was sterile and the illness less acute, but pyæmic abscesses developed.

Under *Group* 5 were classed those rare cases where the blood culture was sterile although there were severe symptoms of toxæmia. Antileucocidin was titrated in one case and was found to be low.

In discussing *treatment*, the authors place great emphasis on excision or drainage of the primary focus, from which the infection of the blood stream is often maintained. Chemotherapy with sulphathiazole (the most effective of the sulphonamides against the staphylococcus) has not been shown to save life in fulminating cases and it does not necessarily sterilize the blood; it may be useful where there are secondary abscesses beyond the reach of surgery, for example in the lungs. Antitoxin with a high antileucocidin titre is recommended in severe cases unless the illness has lasted for 10 days (when the patient's antibodies may be expected to have risen) or unless the patient's antibodies have been titrated and found to be already high.

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HÆMATOLOGY

SPECIAL CONTRIBUTION

RECENT WORK ON BLOOD TRANSFUSION IN BRITAIN

by P. L. MOLLISON, M.B., M.R.C.P.

In the war of 1914–18 the conclusion had already been reached that the most effective single step in the treatment of severe wound shock was the restoration of blood volume by blood transfusion. Inevitably, therefore, great attention has been given to all aspects of this subject in the present war and knowledge has advanced very considerably.

Apparatus.—One of the most important if undramatic advances has been the introduction of a simple standardised apparatus for taking and giving blood by a closed method, that is to say, one in which the blood does not come into direct contact with the open air (*for description, see* Vaughan, 1939). Because of the standardisation there is complete interchangeability of apparatus from all parts of the country, whether produced by the civilian or military services.

Stored Blood.—Storage of blood was practised in only a few hospitals in Britain before the present war. In anticipation of the demands which very heavy air-raids might create, blood banks were established in London at the beginning of the war and in other parts of the country soon afterwards. At first, blood was stored in a simple citrate-saline solution, but soon the observation by Rous and Turner of the beneficial effect of the addition of glucose was confirmed (Harington & Miles, 1939; Maizels & Whittaker, 1940a; Dubash, Clegg & Vaughan, 1940) and a citrate-glucose mixture came into general use. At first, there was naturally much discussion as to the relative merits of stored and fresh blood. Early reports showed, however, that transfusions of stored blood did not give rise to more reactions than those of fresh blood (Stewart, 1940), and that the former were equally efficacious, at least in the treatment of acute hæmorrhage (Brewer, Maizels, Oliver & Vaughan, 1940).

It was realised that the exact value of stored blood could be most satisfactorily measured by estimating the survival rate of the erythrocytes after transfusion, and many workers reported that erythrocytes stored in citrate-glucose mixtures survive well in the recipient's circulation (Bushby, Kekwick, Marriott & Whitby, 1940; Maizels & Paterson, 1940; Mollison & Young, 1940). Many interesting observations were published upon the physical and chemical changes occurring during storage (Maizels & Whittaker, 1939, 1940a, 1940b; Crosbie & Scarborough, 1940, 1941, 1942; Scarborough & Thompson, 1940). Earlier work was confirmed when it was shown that the erythrocytes lose potassium during storage (Downman, Oliver & Young, 1940; Aylward, Mainwaring & Wilkinson, 1940). Maizels & Paterson showed, however, that some at least of these changes were reversible and that stored erythrocytes lost sodium again in the recipient's circulation after transfusion. Some confusion continued to exist as to the best preservative solution and Maizels (1941b) suggested that the laboratory test of measuring the osmotic fragility of stored erythrocytes might give a false indication of the way in which they would survive after transfusion. This point of view was supported by Mollison & Young (1941) who found that although red cells stored in the Rous-Turner solution became very fragile, they survived very well in the recipient's circulation. Conversely, red cells stored in sucrose became very resistant to hæmolysis by hypotonic saline but survived poorly in the recipient's circulation. These workers found that other *in vitro* tests were also misleading, and they therefore undertook a trial of several preservative solutions, using both *in vivo* and *in vitro* tests (Mollison & Young, 1942). They found that the Rous-Turner solution was the best, but considered that its large bulk was too great a disadvantage to warrant its use in preference to the ordinary small volume citrate-glucose solution.

All citrate-glucose solutions have one disadvantage, namely that the citrate and glucose solutions have to be autoclaved separately to prevent the occurrence of caramelisation. Evans, Thorley & McLeod (1942) showed, however, that if the mixture were acidified with carbon-dioxide before autoclaving, caramelisation was prevented. Later, Loutit, Mollison & Young (1943) found that this method was ineffective in their autoclaves, but observed that the addition of citric acid in suitable proportions not only diminished caramel formation but greatly improved the preservative properties of the solution as judged by the survival *in vivo* of the erythrocytes after transfusion. There seems to be little doubt that acidified citrate-glucose mixtures are the most satisfactory blood preservatives yet discovered.

Plasma and Serum.—The only blood substitute available in the last war with an osmotic pressure of the order of human plasma was gum saline, which was eventually shown to have serious disadvantages despite the good immediate results attending its use. Great attention has been given in the present war to the problems involved in using stored human plasma and serum as blood substitutes. In the beginning, the advantage of preparing plasma seemed obvious, since plasma could be obtained as a by-product from stored blood. After MacKay (1941) had shown that none of the available antiseptics could be relied upon to inhibit bacterial growth in liquid plasma in a concentration which would not be toxic if a large transfusion had to be given, it was recognised that plasma stored in the liquid state would have to be Seitz-filtered before storage. It was found, however, that plasma clotted spontaneously after being passed through a Seitz filter. This phenomenon was investigated by Macfarlane, Macsween, Mainwaring & Parish (1942), who showed that, when plasma was passed through a Seitz filter, fibrinogen and prothrombin were at first retained but were present in later samples of the filtrate. It was observed that these later samples were the first to exhibit spontaneous clotting. This clotting could only be prevented by limiting the amount of plasma passed through a given Seitz pad. Even then, its occurrence was not postponed indefinitely. Bushby, Buttle & Whitby (1940) showed that washing of the filter pad with alkali enabled a greater volume of plasma to be passed through one pad before clotting occurred, and this observation was utilised in devising a process for large-scale filtration of plasma. Later, the addition of alkali to the plasma before filtration was advocated (Bushby & Whitby, 1942). In this latter process, the pH was brought back to 7 by mixture with carbon dioxide under pressure. Clegg & Dible (1940) tackled the problem in a different way by calcifying the plasma and then filtering off the clot. Picken (1941) advocated the addition of serum to plasma as a method of precipitating the fibrin. Maizels (1941a) suggested the combination of the two methods in order to reduce the amount of calcium needed and to avoid the necessity for the addition of the large relative volume of serum required in the previous method.

Perhaps the most successful approach to the problem has been made by McFarlane (1942), who has devised a process for extracting the fibrinogen with ether at a low temperature; the resulting product remains clear for very long periods.

Apart from its freedom from fibrinogen, serum has the advantage over plasma that it is more suitable for drying, and since the beginning of the war serum has been dried by a special *Medical Research Council* Unit. In 1940, Adair, Adair & Greaves reported that the osmotic pressure and electric charge of the proteins of human serum were unaffected by the process of drying from the frozen state, and a clinical trial of serum dried in this way proved satisfactory (Brown & Mollison, 1940). The advantages of the dried product have become more and more apparent as experience of the liquid products has accumulated. The most obvious of the advantages are a far greater stability, ability to withstand a wide range of temperature variations, and freedom from the risk of supporting bacterial growths. The process of drying from the frozen state has lately been refined by spinning the bottles as they cool and by "snap-freezing" (Greaves, 1941). In this way an almost amorphous product is produced which has a far greater solubility than the earlier material. Harrison & Picken (1941) have advocated the use of defibrinated blood for transfusion since unwanted blood then directly yields serum.

Shock and Acute Hæmorrhage.—The first trial of plasma transfusions in combating shock in air-raid casualties proved

most successful (Kekwick, Maycock, Marriott & Whitby, 1941). Grant & Reeve (1941) concluded that, in severely injured patients who had lost much blood, the simple measures of rest, warmth and morphine administration were usually insufficient for recovery, but that a transfusion of blood or plasma was a most potent means of restoring or maintaining the circulation. They considered that whether or not there was appreciable hæmorrhage, the great majority of severely injured patients benefited by transfusion. Black (1940) reported good results from treating burns with intravenous plasma.

Volume and Rate of Transfusion.—The modern conception that the amount of blood administered to a patient with anæmia should bear a direct relationship to the degree of increase in hæmoglobin level required, owes much to Marriott and Kekwick. These authors have also urged the importance of administering transfusions at a drip rate. They have advocated (1940) that the rate of transfusions for the relief of anæmia should never exceed 1 cm.^{3} per pound [0·545 kg.] of body weight per hour, and should not exceed half this rate in subjects suffering from severe anæmia, or cardiac or respiratory disease. As emphasised by Whitby (1942), these rules were never intended to apply to transfusions given to accident cases for the restoration of blood volume, and in such cases rapid transfusion is advisable. Whitby mentioned that in 150 cases receiving massive transfusions no single instance of pulmonary œdema was observed. Grant & Reeve (1941) from an analysis of observations on 100 air-raid casualties concluded that early transfusions should be given at the rate of 500 cm.^{3} in 15 to 30 minutes and that later transfusions, unless given to combat further bleeding, should be administered more slowly, namely at the rate of 500 cm.^{3} in one or more hours.

The view that subjects with a normal cardiac muscle will tolerate extremely rapid transfusions was supported by observations made by Sharpey-Schafer & Wallace (1942). Thirteen convalescent subjects received from 700 to 2100 cm.^{3} of human serum intravenously at rates varying between 54 and 168 cm.^{3} per minute. Apart from a transient feeling of constriction in the chest, in some of the subjects, no symptoms or untoward results were observed. A temporary diminution in vital capacity with an increase in the density of the lung shadows and an increase in venous pressure were noted however. Loutit, Mollison & van der Walt (1942) noted that the rise in venous pressure following a transfusion depended rather upon the volume transfused than upon the rate of administration. Sharpey-Schafer & Wallace, whose experience was similar, noted that the rise in venous pressure depended upon the retention of the transfused fluid in the circulation.

Concentrated Red Cell Suspension.—When liquid plasma was first being prepared from stored blood, the possibility of using the residual erythrocytes was explored by MacQuaide & Mollison (1940). At first the erythrocytes were suspended in saline, but later concentrated suspensions were prepared by simply adding together the residues from two bottles of stored blood after removing the bulk of the plasma. Very satisfactory results have since been reported by many authors (Vaughan, 1941; Whitby, 1941; Davidson & Stewart, 1941; Williams & Davie, 1941) using these concentrated erythrocyte suspensions for the treatment of cases of anæmia. An important advantage of their use is the reduction in the total volume of fluid to be administered for the achievement of a given rise in hæmoglobin.

Blood Grouping.—As experience of mass blood grouping has accumulated the possible sources of error have received more attention and the necessity for the use of a reliable technique has been emphasised (War Memorandum No. 9, 1943).

Understanding of compatibility has undoubtedly made its greatest advance since the original discovery of the four blood groups, with Landsteiner and Wiener's discovery of the Rh agglutinogen. This agglutinogen is present in the majority of human bloods and its chief importance lies in the fact that it is capable of provoking the formation of specific immune agglutinins in persons (Rh-negative) whose erythrocytes lack the agglutinogen. The discovery by Levine that Rh-negative women may become sensitised to the Rh agglutinogen during pregnancy when their fœtus is Rh-positive, and the further discovery that the immune agglutinins formed in the mother's circulation may pass back across the placenta and cause *erythroblastosis fœtalis*, have added enormously to the importance of this new finding. These observations have been confirmed by Boorman, Dodd & Mollison (1942), who found that the incidence of the Rh agglutinogen in the English population is similar to that amongst American Whites. They also found, like Levine, that over 90% of the mothers of infants affected with *erythroblastosis fœtalis* are Rh-negative and they described cases in which persons who had become sensitised to the Rh agglutinogen had suffered severe hæmolytic reactions due to the transfusion of Rh-positive blood. Taylor, Race, Prior & Ikin (1942) have described some of the difficulties which may be encountered in making tests for Rh agglutinogens and agglutinins and in particular have drawn attention to the occurrence of zoning in certain anti-Rh sera.

Destruction of Erythrocytes in Vivo.—Application of the technique of differential agglutination, whereby the survival rate of transfused erythrocytes in the recipient's circulation can be estimated quantitatively, is likely to prove increasingly important in the solution of blood transfusion problems. As mentioned above, this method has already been used to decide the question of the value of various solutions for the storage of blood, and the same method is proving invaluable in investigating the new problem of intra-group incompatibility (Mollison, 1943). Transfused erythrocytes should not be eliminated from the recipient's circulation at a rate greater than approximately 1% per day. A study of the causes which lead to an increase in this rate should add much to knowledge of hæmatology in general.

The damage to the recipient's erythrocytes that can be caused by the transfusion of blood, the plasma of which contains high-titre incompatible agglutinins, was studied by Aubert, Boorman, Dodd & Loutit (1942). To simplify the problem, they used plasma of group O rather than blood of group O, and administered it intravenously to subjects of group A. They found that when the plasma contained very potent anti-A agglutinins, samples taken from the recipient immediately after transfusion might show hæmoglobinæmia or intravascular agglutination. Nevertheless, in no case did they produce a really serious reaction.

Summary of Progress.—Investigators in the field of blood transfusion may be said to have achieved important objectives during the present war. The apparatus has been so simplified that transfusions can be given under almost any circumstances. Stored blood can now be kept for periods of 3 weeks or more and still be virtually as efficacious as fresh blood from the point of view of restoring blood volume and of supplying functioning erythrocytes. Stable and satisfactory blood substitutes which can be stored for months or years have been provided. Finally, understanding of transfusion accidents and therefore of the means of preventing them has advanced very considerably.

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[1][*See BMB* 8] [2][*See BMB* 94] [3][*See BMB* 86] [4][*See BMB* 5] [5][*See BMB* 84]

Dr. P. L. Mollison has been working since 1939 *at the South-West London Blood Supply Depôt, one of a number of similar Depôts which have been organised by the Medical Research Council for the Ministry of Health as part of a national blood transfusion service, which supplies the needs both of the civilian population and of the Armed Forces. Dr. Mollison has published, with other members of the medical staff of the Depôt at which he works, a number of papers on various aspects of blood transfusion.*

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THE DETERMINATION OF BLOOD GROUPS

Medical Research Council War Memorandum No. 9, 1943

This memorandum is issued under the authority of a Blood Transfusion Research Committee appointed by the *Medical Research Council*. The technical principles of blood group determination, which must be strictly adhered to if errors in blood grouping are to be avoided, are less widely known than they deserve to be. The objects of the Memorandum are (i) to describe methods which in trained hands have given satisfactory results, (ii) to recommend certain methods, and (iii) to analyse the possible sources of error inherent in all group determinations.

Principles of Diagnosis of the ABO Blood Groups

Two main agglutinogens A and B by their presence or absence in human erythrocytes determine the blood group; the corresponding agglutinins anti-A and anti-B are found in the appropriate human sera. Hæmagglutination occurs whenever homologous agglutinin and agglutinogen are in contact. Unknown erythrocytes are therefore tested for their blood group with known anti-A and anti-B sera. For the most reliable results, however, not only the erythrocytes but also the serum of the unknown are tested, the dual test providing a check on technical and clerical errors.

The Sub-Groups of A

Sub-groups A_1 and A_1B and A_2 and A_2B can be recognised by the fact that the cells of A_2 and particularly of A_2B bloods react more weakly than those of A_1 and A_1B with anti-A test sera. Nearly all anti-A sera from group B and group O donors contain the agglutinins alpha and $alpha_1$. Alpha reacts with all the sub-groups of A while $alpha_1$ reacts only with the sub-groups of A_1 and A_1B. To test for the sub-groups, $alpha_1$ is obtained free from alpha by absorbing anti-A serum with a suitable quantity of A_2 cells. The sera of 1–2 % of A_2 persons and of approximately 25 % of A_2B persons contain the agglutinin $alpha_1$. There is a further agglutinin, anti-O ($alpha_2$), which reacts with all O cells and most A_2 cells. This is found very occasionally in A_1, B, and A_1B sera. A table illustrates the groups and sub-groups with their usually occurring serum agglutinins and possible extra agglutinins.

Methods

(1) *Tube Method.* 0·08 cm.³ of high titre anti-A serum, diluted with an equal amount of normal saline, and a similar quantity of diluted high titre anti-B serum are delivered by graduated Pasteur pipettes into test tubes 2″ × ¼″ [approximately 5·0 × 0·6 cm.]. 0·08 cm.³ of a 5 % suspension of the unknown blood in 3 % sodium citrate is added to each tube. With suitable racks and a standard arrangement of the tubes, large numbers of tests can be carried out simultaneously. As controls, cells of known groups A, B and O should be tested in the same way. The tubes are shaken and left at room temperature for 2 hours. The contents of every tube which does not then show undoubted agglutinates on flicking with the finger are examined microscopically. The agglutinins in the serum are tested for by a similar technique, using known A_1 and B cells. It is important in these tests to look for weak " A " reactions with anti-A serum and to realise that the $alpha_1$ agglutinin can occur in the sera of groups A_2 and A_2B.

(2) *Tile Method.* On a warmed flat white opal-glass tile 0·05 cm.³ of high titre anti-B serum is placed in the left-hand space and an equal amount of high titre anti-A serum in the right-hand space; to each of these is added 0·05 cm.³ of the red cell suspension. The tile is rocked gently to ensure mixing and left to stand for 10–15 minutes. On agitation, agglutination, if present, can be easily seen against the white background. Unknown sera are similarly tested with known cells. Instead of using diluted blood, undiluted blood can also be used, provided that the amount of blood added is sufficient to colour the mixture only a light pink. With this technique the reading should be made in 2–4 minutes. Pseudo-agglutination may occur after this time.

Recommendation 1. The tube method is the most reliable, but where this is found impracticable a tile technique, using diluted blood, is recommended. Undiluted blood should not be used unless the workers have had long experience of the technique.

Recommendation 2. In the case of blood issued for transfusion cells should be examined for an agglutinogens serum for agglutinins. The double check is essential.

Direct Matching

Direct matching of the donor's cells against the recipient's serum before transfusion is extremely important. It should be omitted only in an acute emergency. The technique recommended is fundamentally the same as that already described.

Essential Properties of Test Sera

Serum to be used for blood grouping must fulfil certain conditions. (i) High titre. Only high titre sera, preferably

checked against the *Medical Research Council's* standard, should be used. The standards are available in the dried form. (ii) Capacity to react with A_2 and A_2B cells. Anti-A serum should be titrated in order to determine its capacity to react with A_2B cells. (iii) Absence of cold agglutinins. (iv) Absence of a tendency to cause rouleaux formation. (v) Freedom from fat.

Storage of Test Sera

(i) Temperature: test sera should be kept, if possible, frozen solid. If kept thus their strength is preserved almost indefinitely. If kept at 2–4° C. their strength is preserved for a variable period. (ii) Bulk: serum should be stored in bottles or ampoules which contain amounts suited to the particular needs of the workers who are to use them. A frequent small issue of supplies is more satisfactory than a single large issue. (iii) Asepsis: sterility is important but no antiseptic should be added to test sera. (iv) Dried grouping serum: completely dried serum efficiently sealed in ampoules under nitrogen will keep indefinitely without refrigeration.

Possible Sources of Error in Blood Group Determinations

(*a*) Technical: false negative results may be due to (i) failure to use high titre sera, (ii) failure to use anti-A serum capable of reacting with A_2 and A_2B cells, (iii) failure to recognize the time factor, (iv) the use of infected serum. False positive results may be due to (i) pseudo-agglutination or rouleaux formation, (ii) cold agglutination, (iii) the use of infected cell suspensions, (iv) the use of infected serum. (*b*) Clerical errors: these can be avoided only by careful checking at every stage by everyone concerned.

The Rh Factor

Human erythrocytes may contain in addition to the A and B agglutinogens a variety of antigenic components, of which the Rh factor is the most important. The 15% of English white subjects whose erythrocytes lack this factor are liable to form an agglutinin against this agglutinogen if it is introduced into their circulation. This may occur in pregnancy or with transfusions. Ideally, Rh-negative persons should be transfused only with Rh-negative blood. At present, however, this ideal may be regarded as impracticable.

Tests for Rh Agglutinogens and Agglutinins

Sources of test sera: (i) An animal, preferably the guinea-pig, may be immunized by being given a course of injections of blood from the monkey, *Macacus rhesus*. (ii) Serum may be obtained from a human being who has become immunized to the Rh antigen. Animal sera have to be absorbed [freed from other antibodies acting upon human erythrocytes] but they can be produced at will. With human sera a comparatively large amount can be obtained with little trouble, but may of course contain anti-A or anti-B agglutinins. If necessary, these human sera can be absorbed with A or B Rh-negative blood or neutralized with the appropriate human salivæ [which contain the antigens].

Method

One volume of 2% suspension of blood is placed with one volume of the test serum in a small tube 7 mm. in diameter. It is desirable to test cells with not less than three different sera. At the same time known Rh-positive and Rh-negative cells should be tested against the same sera to act as controls. The tubes should be left for at least one hour and preferably 2 hours in a water bath or incubator at 37° C. The sediments are then examined with a hand lens. When the reaction is negative the sediment is found to be homogeneous and to have a clear-cut circular edge. When the reaction is positive the sediment appears granular and the edge is serrated. When the tubes have been thus examined a little of the sediment in each tube is *gently* withdrawn by means of a Pasteur pipette and *gently* spread on a slide. Agglutinates are seen with those bloods giving a positive reaction. In case of discrepancy between the macroscopic and microscopic appearances it is advisable to rely upon the microscopic finding.

In testing unknown serum for the presence of anti-Rh agglutinins a similar procedure is followed using two known Rh-positive and two known Rh-negative bloods as the test cells.

Some sera containing anti-Rh agglutinins exhibit "zoning." It may therefore be necessary to test serial dilutions of the serum against known Rh-positive bloods.

Recommendations. (i) Mothers of infants manifesting signs of *erythroblastosis fœtalis* should not be transfused with blood unless known Rh-negative blood of suitable ABO group is available. In cases of urgency, plasma or serum may be used instead of whole blood. (ii) Recipients of either sex who are suspected of having become immunized to the Rh-factor should receive no further whole blood transfusions unless Rh-negative blood of suitable ABO group is available. (iii) When transfusions are given to infants affected with *erythroblastosis fœtalis*, blood from a group O Rh-negative donor should be used whenever possible.

Training of Personnel

All blood group determinations should be entrusted only to personnel who have had a sufficient period of training in a laboratory accustomed to such work. The necessity for employing trained personnel is emphasized since there has hitherto been a tendency to consider that anyone can be taught to determine blood groups in a few minutes. It is essential if errors are to be avoided that workers who are making blood group determinations should fully understand the underlying principles of the method.

[*Any workers on blood transfusion who would find the original 17-page Memorandum of value are invited to apply for a copy.*]

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TESTS FOR THE Rh FACTOR AND ITS ANTIBODY

by G. L. Taylor, *Proceedings of the Royal Society of Medicine*, 36, 225–226, March 1943

This paper, which reports work done by the author on behalf of the *Medical Research Council* at the *Galton Laboratory* Serum Unit at Cambridge, cannot be much abbreviated and is reproduced below with only a few modifications and omissions.

The presence of Rh antigen in the erythrocytes is detected by agglutination on addition of serum containing the corresponding anti-Rh agglutinin. Grouping sera are obtained (i) from the rabbit or guinea-pig injected with rhesus monkey erythrocytes; (ii) from mothers of erythroblastic infants or from persons who have had hæmolytic transfusion reactions due to Rh.

The preparation of animal sera is difficult. Few human sera are strong enough, but they will, in the author's opinion, probably prove to be the most convenient, and will be prepared from the mothers of erythroblastic babies.

Detecting anti-Rh. Serum is heated for fifteen minutes at 56° C., and is then mixed with cells from at least two strongly positive donors, with negative cells, and with cells from the donor of the serum; some sera agglutinate their own cells and this is a necessary control. Known positive and negative cells should be of group O to avoid the possibility of reactions due to the A–B–O system of groups. Most grouping is done on a slide, tile or plate, but for Rh work tubes must be used. The author's tubes are 2 inches long by ¼ inch in diameter [approximately 5·0 × 0·6 cm.], and in them a series of falling dilutions of serum is prepared. In the first tube the serum is undiluted; in the second diluted 1 : 2; in the third 1 : 4 and so on for 6 or 7 tubes. To each tube is added a volume of erythrocyte suspension (1 to 2% whole blood) of a strongly positive donor. Cells and serum are mixed by picking up a tube and flicking with the finger, and on each tube is placed a glass cap to prevent evaporation and serve as place-marker in reading tests. To other identical series are added cells from a second strongly positive person, negative cells, and the cells of the donor of the serum. If the donor is the mother of an erythroblastic baby, if the A–B–O groups permit, and if the cells are available, the serum is also titrated with cells from the baby and the father. The tests are stored at room temperature and an identical set in the incubator at 37° C. Some human anti-Rh sera work better at room, others at body temperature. The great majority are better at body than at room temperature.

After an hour, or better after two, the tests are read. The character of the sediment at the bottom of the tube gives a good idea as to whether there is clumping or not. The cap is removed and the sediment examined with a hand lens, but the final diagnosis is based on microscope examination. The greatest care and gentleness are needed in transferring some of the sediment to a microscope slide; any roughness may undo some of the more weakly positive reactions and a false negative may be recorded. Good reactions are easily seen; weakly reacting cells may cause trouble. In rouleau-forming, cells aggregate, and a beginner may mistake [illegible]

true agglutination a lumpy aggregation of cells; such an aggregation gradually breaks up. The author recommends this procedure because (i) titration indicates the strength of any antibody present, (ii) one serum, when undiluted, failed to react with some positive cells but, in titration, gave definite reactions in some dilutions.

When tests suggest that anti-Rh is present, the serum is mixed with positive cells from four or five other donors and with one or two lots of negative cells, and if it reacts with all or nearly all the positives and not with any negatives, it seems certain that anti-Rh is present. Indeed, when all the positives react and the negatives fail to, a simple sum gives exactly the odds that the serum contains anti-Rh. The author advises this titration technique in direct compatibility tests between recipient's serum and potential donors' cells.

With good sera, erythrocytes can be grouped for Rh by methods similar to those described. Titration is not needed and a serum which required titration would not be used. A volume of serum is mixed with a volume of erythrocytes and to avoid any tendency to give false agglutination, a volume of saline is added. Tests are stored at room or incubator temperature according to which is better for the sera in use. Bringing together antibodies and antigens of he A–B–O groups should be avoided, otherwise the Rh grouping cannot be done. Anti-A or anti-B in a serum can be absorbed by mixture with appropriate cells, *e.g.* A Rh-negative cells will remove anti-A and leave anti-Rh. Mixing the serum with the saliva of a person who secretes the appropriate antigen will also remove the A–B–O antibodies. About 80 % of people secrete in the saliva the A-B-O antigens present in their red cells. If a supply of Rh sera from all the four blood groups is available, there is no need for absorption.

No cells should be diagnosed as negative unless they have been tested with at least three strong anti-Rh sera. Some sera react well with all but a few Rh-positive cells. One may react well with the cells of x and poorly or not at all with those of y, whilst another does well with y and badly with x. If a serum tends to give slight false positive reactions, reference to the reactions given by other sera will help diagnosis.

Rh testing is difficult and needs considerable experience, but it will become less of an art and more of a science when ood supplies of really strong sera are available, and these ust come from the clinicians who are in charge of the mothers of erythroblastic babies.

In the author's unit, blood from 49 mothers of erythroblastic babies has been examined; 43 were Rh-negative, and in the sera of 37 of these, anti-Rh was found. In a random sample of 49 women only 7 or 8 would be expected to be Rh-negative. There can be no doubt that the Rh factor plays an essential part in the causation of most cases of *erythroblastosis fœtalis*.

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THE INVESTIGATION OF HÆMOLYTIC TRANSFUSION REACTIONS

by P. L. Mollison, *British Medical Journal*, **1**, 529–532 & 559–561, 1 5/43 & 8/5/43

This paper is a Report to the *Medical Research Council* from the South-West London Blood Supply Depot.

A hæmolytic transfusion reaction may be defined as the occurrence of an abnormal destruction of the red cells of either the donor or the recipient immediately after transfusion.

Following a normal compatible transfusion of fresh blood, the donor's erythrocytes are destroyed only at a slow rate. Approximately 1% are eliminated each day. When incompatible blood is transfused, however, the donor's erythrocytes are rapidly destroyed. A similar rapid destruction occurs when blood which has been stored for an excessive length of time is transfused. Destruction of some of the recipient's own red cells may follow the transfusion of blood, the plasma of which contains high titre agglutinins incompatible with the recipient's red cells.

When transfusions are given to persons affected with certain varieties of hæmolytic anæmia the signs of hæmolysis may temporarily become more pronounced. Such reactions may not be due to any of the causes enumerated above.

The establishment of the diagnosis of a hæmolytic transfusion reaction depends (*a*) on the demonstration of increased blood destruction and (*b*) on the demonstration of the cause.

Signs of Increased Blood Destruction

Intravascular destruction results in the liberation of hæmoglobin into the plasma. This hæmoglobin may be eliminated in three different ways (Fairley, 1940): (i) It may be absorbed by the reticulo-endothelial system and converted to bilirubin. (ii) The hæmoglobin is broken down intravascularly. Hæmatin is formed and this combines with serum albumin to form methæmalbumin. (iii) Some hæmoglobin is excreted by the kidney, but only when the concentration in the plasma exceeds approximately 135 to 180 mg. per 100 cm.^{3} (Gilligan, Altschule & Katersky, 1941). When the urine is alkaline, most of the hæmoglobin will be in the form of oxyhæmoglobin. If the urine is neutral or acid, methæmoglobin will be formed. Hæmoglobinuria is always accompanied by albuminuria and sometimes by glycosuria. Some degree of renal failure may occur.

Extravascular destruction of erythrocytes results in the production of bilirubin. The degree of bilirubinæmia depends upon the rate of blood destruction and upon the efficiency of the liver in removing the bilirubin from the bloodstream.

When, as the result of intravascular or extravascular destruction, the serum bilirubin concentration exceeds approximately 4 mg. per 100 cm.^{3}, the recipient becomes jaundiced. Slow blood destruction is less likely to produce jaundice. The liver function may be impaired by the transfusion of incompatible blood. Evidence of liver damage is sometimes apparent at necropsy and may be manifested during life by the development of signs of toxic jaundice.

Because of the blood destruction, the increase in hæmoglobin concentration expected as a result of transfusion does not occur when there is a hæmolytic reaction.

Apart from the signs of increased blood destruction, the recipient may show signs of constitutional disturbance. A rise in temperature, with or without a rigor, is common. Severe lumbar pain and other symptoms, such as burning of the face, tightness of the chest, *etc.*, may occur. Some degree of collapse is common. These symptoms and signs may be delayed or may be entirely absent. Conversely, they may be produced by the transfusion of apparently compatible serum. There is an impression that the sequelæ of transfusion of incompatible blood are less severe now than formerly. This may be due to the increasing tendency to administer blood at a slow drip rate.

Destruction of Incompatible Blood

In vitro, incompatible red cells may be either agglutinated or hæmolysed by the recipient's plasma. *In vivo*, intravascular hæmolysis may occur, when only agglutination occurs *in vitro*. This is especially the case when the incompatibility involves the Rh factor.

After the transfusion of incompatible blood, clumps of agglutinated cells may be found in blood samples withdrawn from the recipient. These agglutinates may persist for at least 48 hours after transfusion. When the recipient has, at the time of the transfusion, plasma agglutinins incompatible with the donor's erythrocytes, the majority of the donor cells are eliminated within a few hours of transfusion. In such cases the recipient's plasma agglutinins undergo characteristic changes in titre (Rö, 1937; Wiener, Oremland, Hyman & Samwick, 1941; Mollison & Young, 1941). There is usually an initial reduction in titre followed by a rapid increase which reaches its peak 10–20 days after transfusion. When the recipient's plasma does not actually contain incompatible agglutinins, but there is a potential incompatibility as when Rh-positive blood is transfused to an Rh-negative recipient, the rate of elimination is variable. If the recipient fails to react to the stimulus of the foreign agglutinogen of the donor blood, the latter may survive perfectly normally. If the recipient does respond by producing anti-Rh agglutinins, the total survival of the donor cells is reduced. The term "inapparent hæmolysis" has been applied by Wiener to such cases of slow destruction after transfusion.

Destruction of Stored Blood

The rate of destruction of the erythrocytes of stored blood in the circulation of a normal recipient after transfusion depends upon (i) the length of storage of the blood, (ii) the preservative solution used, and (iii) the temperature of the storage. The erythrocytes of blood stored at 5° C. for periods up to 21 days in a citrate-glucose diluent (*M.R.C. War Memorandum* No. 1, 1940) survive well during the 24 hours after transfusion. Erythrocytes of blood stored

in a simple solution of sodium citrate, however, survive far less well, and after 17 days of storage are almost completely eliminated from the recipient's circulation within 24 hours of transfusion (Mollison & Young, 1942).

Destruction of Recipient's Red Cells by High-titre Incompatible Agglutinins

Intravascular agglutination and hæmolysis followed by bilirubinæmia have been produced experimentally by the injection of plasma containing high-titre incompatible agglutinins (Aubert, Boorman, Dodd & Loutit, 1942).

Hæmolytic Reactions in Persons affected with Hæmolytic Anæmias

An illustration of such reactions is seen in a case reported by Dacie & Firth (1943). The transfusion of agglutinin-free plasma resulted in hæmoglobinæmia. The transfusion of a concentrated suspension of red cells brought about a violent hæmolytic reaction, although the donor cells survived normally.

Hæmolytic Reactions simulated by the Transfusion of Hæmolysed Blood

Blood may become hæmolysed by the action of contaminating organisms, by being overheated, or by being stored for excessive periods under unsuitable conditions. The transfusion of such blood may give rise to phenomena indistinguishable from true hæmolytic reactions as defined above.

Investigation of Hæmolytic Reaction

The investigation is greatly facilitated if certain samples are available. These are (i) a sample of the donor's blood, (ii) a pre-transfusion sample of the recipient's blood, (iii) a sterile sample of blood from the recipient after transfusion, and (iv) a clean sample of urine. The third sample should be partitioned into two plain tubes (one sterile), and one tube containing dry oxalate.

Examination of the Samples

In any case some or all of the following tests may have to be made :

(*a*) *Donor's blood.* (i) Bacteriological examination ; (ii) estimation of free hæmoglobin in the supernatant plasma ; (iii) regrouping, testing both cells and plasma ; if necessary, Rh typing ; (iv) cross-matching of the cells against the recipient's pretransfusion serum sample ; (v) the titre of the agglutinins in the donor's plasma.

(*b*) *Recipient's blood.* (i) Bacteriological examination of the sterile sample ; (ii) estimation of free serum hæmoglobin and serum bilirubin ; examination for methæmalbumin ; (iii) serological tests—a 2% suspension in isotonic citrate of the oxalated sample is examined for the presence of free agglutinates ; regrouping, testing both cells and plasma and, if necessary, Rh typing and examination of the plasma for anti-Rh agglutinins ; titration of the agglutinins in the plasma for comparison with the results of titrations on later samples ; if necessary, differential agglutination tests to determine the proportions of recipient and donor blood.

(*c*) *Urine.* (i) Routine tests ; (ii) special tests for pigments, pigment casts and urobilin.

Preliminary regrouping of the blood of the donor and recipient may reveal a mistake in ABO grouping. In such cases, four of which are described in the original paper, no other tests will be necessary. Rh typing and cross-matching may reveal incompatibility, and, here also, four illustrative cases are described. Another case instanced is that in which a hæmolytic reaction was simulated by the transfusion of hæmolysed blood ; in a further case, there was a fatal reaction due to the transfusion of infected blood.

Two other cases of which particulars are given by the author show that transfusion reactions, thought to be due to hæmolysis of the donor blood, were actually not so, as the survival of the donor's erythrocytes was proved by differential agglutination.

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[1][*See BMB* 89]

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I. THE MECHANISM OF RED BLOOD CELL DESTRUCTION

by B. G. Maegraith, N. H. Martin & G. M. Findlay, *British Journal of Experimental Pathology*, **24**, 58–65, April 1943

II. LYTIC AGENT AND INHIBITORY FACTORS IN HUMAN TISSUE AND SERA

by B. G. Maegraith, G. M. Findlay & N. H. Martin, *Lancet*, **1**, 573–575, 8/5/43

I. These two papers mark an advance of fundamental importance in the study of hæmatology. The precise mechanism by which red blood cells are destroyed in the body has not previously been described, although it has been vaguely assigned to the reticulo-endothelial system. It is now shown to be due to a specific enzyme present in the tissues of many organs. The activity of this enzyme is normally controlled by the presence in the serum, and possibly also in the tissues, of an inhibitory substance. This inhibitor, unlike the lytic enzyme, is not species-specific. The rate of erythrocyte destruction in the body is therefore controlled by the balance between these two substances.

The lysin present in the tissues was demonstrated by incubating suspensions of washed erythrocytes in buffered glucose-saline with small washed slices of the tissue concerned. After the lapse of 12 hours or more, hæmolysis began to occur and was maximal between the 18th and the 24th hour. In controls without a tissue slice, or with tissue which had previously been heated to 80° C. for 5 minutes, there was no lysis. When these experiments were repeated with serum present as well in a dilution of 1 : 100, lysis did not occur. An inhibitory substance was therefore present from the serum. Titration of this inhibitor showed that it was effective at high dilution, in some cases even up to 1 : 1280. Experiments on these lines were done with the blood and tissues of guinea-pigs, monkeys and man. In each case similar results were obtained. When, however, the tissues of one species were incubated with red cells of another species there was no hæmolysis. The lytic enzyme is therefore species-specific. Serum from any of the animals under test would, however, prevent lysis in the tissues and erythrocyte systems of any of the other animals. This showed that the inhibitor was not species-specific. The enzymatic nature of the lysin was inferred: from the time relations of the reaction, from its inactivation by gentle heat, and from the fact that its action could also be prevented by minute traces of mercuric chloride or potassium cyanide, both of which are well-known enzymatic poisons. The final proof of the enzymatic nature is still lacking, as the authors themselves are careful to point out, but there seems to be little doubt that this will be forthcoming when the experiments can be repeated and extended in a laboratory where the necessary facilities are available [the work now reported was carried out in a military laboratory overseas].

II. In the second paper the authors describe how the technique of demonstrating this inhibitor in serum was used to investigate some cases of blackwater fever. During the stage of acute hæmolysis, a substantial reduction in the titre of the inhibitor was found. On recovery the titre rose again to normal values.

In their discussion of these results the authors suggest " that at least one of the factors involved in the development of the abnormal degree of lysis in blackwater fever is a reduction in the activity of the circulating inhibitor, with the result that in blackwater fever the balance between the tissue lytic agent and the inhibitory factor is upset in the direction of lysis. This amounts to saying that in blackwater fever there exists no abnormal lysin ; rather the lysis is simply a manifestation of excessive uninhibited activity of a normal lytic process."

The technique described in these papers should be of use in future investigations into all the hæmolytic anæmias and may well result in a substantial increase in our knowledge of these obscure and fascinating diseases.

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SURVIVAL OF NORMAL ERYTHROCYTES AFTER TRANSFUSION TO PATIENTS WITH FAMILIAL HÆMOLYTIC ANÆMIA (ACHOLURIC JAUNDICE)

by J. V. Dacie & P. L. Mollison, *Lancet*, **1**, 550–552, 1/5/43

Very few attempts have so far been made to estimate the survival time of transfused blood in cases of familial hæmolytic anæmia, although important evidence might thus be obtained as to the mechanism of the hæmolytic process in this disease. A method of estimating the survival of transfused erythrocytes by means of differential agglutination was first applied to man by Ashby (1919), who showed that after transfusing blood of group O to a recipient of another group, say A, the recipient's cells could be agglutinated with anti-A sera and the unagglutinated group O cells (of the donor) could then be counted. Wiener (1934) and Mollison & Young (1942) both found that after transfusion the donor erythrocytes are steadily eliminated from the (presumably "normal") recipient's circulation over a period of 80–120 days, the average being 109 days. Various workers have estimated the survival of transfused blood in isolated cases of hæmolytic anæmia, but lack of certainty as regards the diagnosis, or technical difficulties, have marred their observations in most cases.

Lloyd (1941), basing his estimates on a study of the cell-diameter distribution curves after transfusion, found that in one of 2 patients afflicted with familial hæmolytic anæmia the transfused cells seemed to have disappeared by the fourth week and in the second case they survived for at least 17 days after transfusion. In cases in which the donor cells are of normal diameter and those of the recipient vary widely in diameter, as in the disease in question, it seems difficult accurately to study, by this method, the survival of the normal cells after a large proportion of them has disappeared. A modified Ashby's technique which, being independent of morphological differences, does not suffer from this disadvantage, was used by the present authors, from the Central Pathological Laboratory, Sector IX, and the South-West London Blood Supply Depot respectively, to estimate survival time in 6 cases. Five of these (cases 2, 3, 4, 5 and 6, aged 72, 45, 43, 41 and 9 years) with a family history of the disease, had suffered from anæmia and jaundice for many years, while in the sixth (case 1), an infant aged 1 year, the disease had been manifest since the age of 2 months.

In all 6 cases group O blood was used for transfusion (in case 3 the recipient belonged to group O and in the other cases to group A), and blood samples were withdrawn from the recipient before and immediately after the transfusion, on the following day, and then at intervals (usually every 14 days) until the experiments were terminated. Cases 2–6 received a concentrated cell suspension prepared from two or more bottles of blood stored in citrate-glucose for a few days (according to Mollison & Young, 1942, the survival of such blood in healthy subjects should be normal), and case 1 was given defibrinated blood previously stored for 24 hours. Since the use of large amounts of blood for transfusion greatly increases the accuracy of the Ashby method an initial concentration of between 800,000 and 2,200,000 donor cells per mm.^{3} was produced in the recipient's circulation.

Ashby's original technique has proved unsatisfactory even with the high titre sera necessary to obtain complete agglutination of the recipient's erythrocytes, and various modifications can be employed with advantage (Mollison & Young, 1940). With a view to shortening the time necessary for full agglutination, and to improving agglutination without impairing the accuracy of the method, in these experiments the mixture of cells and serum was centrifuged at approximately 1500 revolutions per minute for 1 minute. The test-tubes containing the mixture were agitated to break up the sediment and free the unagglutinated cells, centrifuged once more, and again shaken. With anti-M and anti-N sera centrifugation cannot be employed because it usually causes some non-specific agglutination unless the sera have been more fully absorbed than usual. In such cases, therefore, the mixtures of cells and serum are allowed to stand for 2 hours in small flat-bottomed bottles of such a size that the mixtures are spread out in a thin layer.

In 5 out of the 6 patients with familial hæmolytic anæmia the rate of disappearance of the donor cells was normal and the total survival time was between 100 and 130 days. In case 3, however, destruction was more rapid, and was complete in about 60 days. Further study revealed that this patient was Rh-negative (the other 5 were Rh-positive), whereas the donor blood was Rh-positive and, following its disappearance, anti-Rh agglutinins appeared in the patient's serum.

A series of subsidiary experiments in which the survival time of blood taken from case 4 and transfused into patients with mild secondary anæmias was estimated by the method of Mollison & Young (1940), showed that blood taken before splenectomy was completely eliminated within 14 days of transfusion, while normal blood given to the same recipient at the same time survived normally. Blood taken from case 4 a year after splenectomy again rapidly disappeared from the circulation of a normal recipient after transfusion, only 32 % of the donor cells being present at the end of 8 days, while destruction was complete within 19 days.

The authors conclude that these observations support the theory that the basic abnormality in familial hæmolytic anæmia is the formation of erythrocytes with an increased tendency to hæmolysis and cannot be reconciled with any hypothesis assigning a major role to abnormal destructive mechanisms.

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BLOOD TRANSFUSION IN NOCTURNAL HÆMOGLOBINURIA

by J. V. Dacie & D. Firth, *British Medical Journal*, **1**, 626–628, 22/5/43

Chronic hæmolytic anæmia with nocturnal hæmoglobinuria (the Marchiafava-Micheli disease or "nocturnal hæmoglobinuria") is an uncommon type of hæmolytic anæmia for which there is no specific treatment and which, although variable in cause and severity, ultimately proves fatal. It seemed possible from the observations of Ham (1939), who reported remissions after transfusion in spite of an initial severe hæmolytic reaction, that blood transfusion might have an inhibitory effect on hæmolysis, perhaps owing to the presence of a naturally occurring antihæmolytic substance in the transfused blood (Josephs, 1938). The present authors, a Pathologist in the *Emergency Medical Service* and the Senior Physician to *King's College Hospital*, London, respectively, record the results of an experiment to determine whether this hypothetical inhibitory effect might prove to be a basis for an effective line of treatment.

The subject of the experiment, a thirty-eight year old woman who had suffered from anæmia and abnormal discoloration of the urine passed in the early morning since November 1940, was admitted to hospital with jaundice on July 1st, 1942. The tentative clinical diagnosis of nocturnal hæmoglobinuria was confirmed by serological tests which revealed: (i) that a proportion of the patient's cells were lysed *in vitro* after 1 hour's incubation at 37° C. in autogenous fresh serum or that of normal subjects of the same group; (ii) that lysis was sensitive to changes in pH, and was increased by the addition of fresh guinea-pig serum from which all anti-human heterolysin had been absorbed; (iii) that the patient's cells were not lysed by guinea-pig serum in the absence of human serum; and (iv) that normal cells were not lysed by the patient's serum under any conditions.

After 3 weeks' observation, therefore, 2 litres of stored (6 weeks-old) filtered human serum were administered intravenously within 12 days. After each bottle of serum, gross hæmoglobinæmia and hæmoglobinuria occurred, followed by a period of freedom only interrupted by administration of a further bottle. The urine remained clear for 10 days after the last bottle of serum was given on September 1st, but laboratory investigations revealed no significant changes in Hb or in erythrocyte number per mm.^{3}, and a standard *in vitro* test showed no alteration in the sensi-

tivity of the patient's cells to hæmolysis by her own serum. No evidence was thus obtained to support the hypothesis that an antihæmolytic factor was lacking. On September 11th the patient was given 500 cm.³ of a concentrated cell suspension of Group O citrate-glucose blood within 90 minutes. Before the transfusion had been quite completed symptoms of a hæmolytic reaction began to be felt. These grew more severe during the following night, but subsided within 24 hours and by September 15th the specimens of urine passed were clear. The period of remission which ensued lasted for 6 weeks. Laboratory investigations showed that during the hæmolytic episode more than half of the patient's own erythrocytes were destroyed while the survival of the transfused blood was unimpaired. The ultimate rise in blood count, which coincided with the remission from hæmoglobinuria, was due to the good survival of the transfused cells, for the patient's own cells did not rise in number above the pre-transfusion level.

The authors conclude that these observations support the hypothesis that the basis of this strange disease is an undefined abnormality of the patient's erythrocytes which causes them to hæmolyse in the presence of human serum both *in vivo* and *in vitro* (*see* Ham & Dingle, 1939). The possibility that the patient's erythrocytes were sensitised by the presence of an immune body or other hæmolytic agent would appear to be negatived by the unimpaired survival of the transfused normal cells.

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FAMILIAL HÆMOLYTIC ANÆMIA (ACHOLURIC JAUNDICE), WITH PARTICULAR REFERENCE TO CHANGES IN FRAGILITY PRODUCED BY SPLENECTOMY

by J. V. Dacie, *Quarterly Journal of Medicine*, 12, 101–118, April 1943

The nature of familial hæmolytic anæmia, or acholuric jaundice as it is sometimes called, is still obscure, but it is to be hoped that the increasing use of exact methods of research, such as have been applied to it in 24 cases reported by the author of this paper, will help to solve the problem.

The criteria that he accepts for diagnosis are:

" An anæmia of hæmolytic type with increased susceptibility of the erythrocytes to hæmolysis by hypotonic saline, spherocytosis, an abnormal tendency of the blood to lysis *in vitro* on incubation at 37° C., and splenomegaly in which engorgement with blood is the outstanding feature. A history of recurrent anæmia or jaundice over a period of years and a positive family history have been taken as confirmatory, though not essential for diagnosis."

The technique for estimating fragility was devised by Creed (1938) and modified by Dacie & Vaughan (1938). Briefly it consists in preparing a series of tubes containing progressive dilutions of sodium chloride, each differing by 0·02%. Blood is added to each tube and the degree of hæmolysis that occurs is estimated colorimetrically. The results are plotted graphically. The normal curve is steep and smooth, hæmolysis beginning at about 0·5% NaCl and being complete at about 0·36%. Curves of this type were found in 5 of the 24 cases studied. In 12 cases a " tailed " curve was obtained. This is a curve which follows the normal closely in the lower dilution range, but is prolonged above 0·5%. Some hæmolysis may even be detected up to about 0·7% NaCl. A third type of curve, found in 6 cases, is called the " diagonal " type. This is almost a straight line, sloping evenly from about 0·7% to 0·4%; it nowhere approximates to the normal curve and presents a great contrast to it.

Splenectomy was performed on 12 cases, 7 of which had " tailed " curves before operation; 24 hours later there was a slight increase in the mean fragility, but this later fell to normal, and by the 10th day after operation the curves were nearly normal in shape. Two cases in which there were " diagonal " curves before splenectomy showed a decrease of fragility afterwards, but the curves, though altered, did not become absolutely normal.

The transient post-operative increase in fragility may have been due to the effects of the anæsthetic. The later decrease may have been due either to the removal of an organ which increased erythrocyte fragility, or to the production by the bone marrow of a more resistant type of erythrocyte as a result of the diminished rate of hæmolysis after splenectomy.

Histologically, the excised spleens all showed the well-known features of this disease: distension of the pulp with erythrocytes, small sinuses with endothelial nuclei often protruding into their lumina, absence of obvious erythrophagocytosis and of hyperplasia of the reticulum cells, presence of unusual amounts of iron-containing pigment and fibrosiderotic nodules.

Some experiments were done to try to find the cause of the engorgement. Perfusions, at 100 mm. Hg pressure, first with saline and then with suspensions of the easily recognisable fowl erythrocytes were done on some of these spleens as well as on some normal controls. The experiments showed that there was no obstruction to these cells in their passage through the direct pathways between capillaries and sinuses. Nevertheless it is more difficult to free the abnormal spleens of erythrocytes by saline perfusion than it is to wash the cells out of normal organs.

Spherocytosis, a term indicating the presence of erythrocytes smaller in diameter but of abnormal thickness, is a constant feature of this disease. It is not yet settled whether this represents a primary disturbance of erythropoiesis, or whether it results from the presence of an abnormal hæmolytic agent or mechanism. The author inclines to the former view after a discussion of the various hypotheses put forward by many other writers.

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EFFECT OF THE pH OF THE BLOOD ON HÆMOLYSIS: With Special Reference to Blackwater Fever

by F. Smith & R. W. Evans, *British Medical Journal*, 1, 279–282, 6/3/43

This paper is by a physician and a pathologist now working with the British Army in a malarial district overseas. Sixteen cases of blackwater fever were studied with the object of finding the cause of the intravascular hæmolysis so that a logical remedy could be applied.

The authors first found that in normal people there is a wide variation in the erythrocyte fragility throughout the course of the day. In samples taken at hourly intervals for 24 hours the erythrocytes were more fragile at night than during the day. It was shown by Dacie, Israëls & Wilkinson (1938) that the pH of the blood is lower during sleep at night than it is in the daytime. The present authors also found that the erythrocyte fragility was much affected by the pH of the diluting fluid used. The more acid the fluid the more fragile the cells became. In patients with blackwater fever the erythrocytes were more fragile than in normal controls.

In all cases studied the fever started with a rigor and was preceded by a sense of intense fatigue for 2 or 3 days. Vomiting was also a constant feature. In this disease a man may lose the equivalent of 2 to 3 litres of blood by intravascular hæmolysis in 36 hours. The clinical picture therefore has much in common with " shock " and so has the treatment.

Sections of the kidney show blockage of the tubules. This used to be thought due to crystals of acid hæmatin but is more likely due to methæmoglobin and cellular debris. Treatment must aim at preventing or lessening the renal blockage. Five factors are considered with the treatment appropriate to each.

Factor A. The hæmolysis: The experiments already mentioned indicate that sufficient alkali must be given to raise the pH of the blood. This will render the cells less fragile and hæmolysis will cease. For rapid effects 20 cm.³ of a 2M or 3M solution of sodium lactate can be given intravenously every 8 hours. The solution can be sterilised by boiling, but is rather apt to cause thrombosis of the vein into which it is injected. Less rapid effects are obtained by giving by mouth every 2 hours 1·3 g. of sodium bicarbonate and 1·3 g. of sodium citrate in 15 cm.³ of water.

Factor B. The obstruction of the renal tubules by the products of hæmolysis: Sweating may account, in the Tropics,

for half the fluid output of the body. It leads to concentration of the urine and is therefore dangerous when the renal function is impaired. Tepid sponging should therefore be ordered when the temperature exceeds 103° F. [39·5° C.]. The fluid balance should be carefully recorded; provided that two-thirds of the intake is excreted by the kidneys the chance of recovery is good. Excess of fluid given intravenously is dangerous as it may lead to generalised œdema.

Factor C. The severe degree of anæmia, damaging the kidneys' excretory function: The erythrocyte count often falls to 2,000,000, while the leucocytes rise. Blood transfusion is often advocated, but the present authors advise caution in its use. Patients are liable to have exceptionally severe transfusion reactions, so that particular care in doing the compatibility tests is needed. Double cross-matching at room temperature and also at 4° C. for 24 hours should always be done. Even with blood that is quite compatible the transfusion should be started very slowly, only 20 drops being given in the first 10 minutes, after which the rate may be increased. Later, when the urine is clear, iron therapy should be started.

Factor D. The production of acid hæmatin crystals in the renal tubules: The high degree of alkalinisation will prevent this from occurring.

Factor E. The existence of living malarial parasites in the blood: The fact that the patient is still suffering from malaria should not be forgotten. Half a tablet of mepacrine (atebrin) should be given 48 hours after the hæmoglobinuria has ceased. If there are no ill effects from this, continue with half a tablet twice a day for a week and then two tablets every third or fourth day.

Summary: In this paper the claim is made that erythrocyte fragility varies from hour to hour and is related to the pH of the blood. The authors were unable to determine the pH of the samples tested for fragility. This was because the apparatus was not available, owing to service conditions, for performing the tests with sufficient accuracy. The good effect of massive alkaline therapy goes far to support their claim. Of the 16 patients seen, those receiving alkali did better than those not so treated.

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HÆMOGLOBINOMETRY AND THE USE OF THE HÆMATOCRIT: A Report to the Traumatic Shock Committee of the Medical Research Council

British Medical Journal, **1**, 209–212, 20/2/43

For some years interest has been renewed in the problem of "wound shock." With the development of blood transfusion technique on a large scale, and especially the introduction of plasma transfusion, great advances in the treatment of this condition were made. It was nevertheless apparent that much research was still needed and the *Medical Research Council* accordingly appointed a committee to investigate "traumatic shock." As this body soon found that progress was hindered by the lack of uniformity of methods for estimating the various constituents of the blood, a sub-committee was appointed to report on the methods in use. In the present report, the findings and recommendations of this sub-committee are set forth.

The complexity of hæmoglobin chemistry is first briefly considered. In normal venous blood, hæmoglobin exists mainly in two forms—oxyhæmoglobin (O_2–Hb) and reduced hæmoglobin (Hb). Up to 3 % of methæmoglobin (met–Hb), formed by the reduction of the ferrous iron in O_2–Hb or Hb, may also be found in normal blood. In city dwellers or heavy smokers up to 3 % of carboxyhæmoglobin (CO–Hb) may also be present; it is 210 times more stable than O_2–Hb and does not carry oxygen. In carbon monoxide poisoning 20 to 50 % of the total Hb may be CO–Hb. During treatment with certain drugs, especially sulphanilamide, both met–Hb and sulphæmoglobin (S–Hb) may be found in appreciable quantities. Neither of these compounds carries oxygen to the tissues. It is the simultaneous presence of several of these compounds that gives rise to the difficulties of hæmoglobin estimation.

There are five types of methods used for hæmoglobin estimation: (*a*) Those involving gas analysis are accurate in experienced hands but are not suitable for general use. They measure the oxygen capacity of the blood. (*b*) Colorimetric methods are those in which the colour developed in the test solution is compared with a standard. In (*c*) photo-metric and (*d*) photo-electric methods it is the amount of light passed by the solution that is estimated. Both types are subject to several sources of error of which the human factor is one. The error is eliminated in the photo-electric methods in which the amount of light transmitted is measured by a photo-electric cell. The cell itself, however, introduces other errors. The fifth type consists of (*e*) methods for estimating the iron content of well washed lysed red cells. The sub-committee regards this as the best check on all other methods and prefers the method of titration of ferric iron with titanous sulphate (Klumpp, 1934).

For all estimations, venous blood taken without stasis is recommended, although if it is necessary to use capillary blood the ear should be punctured rather than the finger.

As there was a lack of standardisation in the instruments commercially available the sub-committee sought the help of the *British Standards Institution.* Together they investigated and standardised the Haldane-Gowers hæmoglobinometer, a well-known and simple instrument in which CO–Hb is used. They recommend the use of instruments that conform to their specification B.S. No. 1079–1942. In this the forms of pipette, dilution tube and colour tube have been accurately defined. Instruments can be tested for conformity with this standard by the *National Physical Laboratory.* It is hoped that the adoption of this standard may lead to that uniformity which is essential if hæmatological results are to be compared. Where CO is not available the acid hæmatin method of Sahli should be used. The *British Standards Institution* propose to standardise this instrument too. The sub-committee emphasises that the standard now proposed is only an *interim* standard until a more satisfactory one, related to the total hæmoglobin in normal human blood, has been defined.

The hæmatocrit is used to determine both the relative proportion of cells to plasma and also the total volume of red cells in a known volume of blood. From this, knowing also the total red-cell count, the mean corpuscular volume of the red cells may be calculated. The method of Wintrobe & Landsberg (1935) is recommended.

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[A full discussion of many of the points mentioned in the report summarised above is given by J. W. Clegg & R. G. Macfarlane (1941) in an unpublished *Medical Research Council Memorandum on the Estimation and Standardisation of Hæmoglobin.*]

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STANDARDISATION OF THE HALDANE HÆMOGLOBINOMETER

by R. Donaldson, H. G. W. Harding & G. Payling Wright, *Journal of Pathology and Bacteriology*, **55**, 205–215, April 1943

The importance of standardisation of methods for estimating the hæmoglobin content of blood has recently been emphasised in a Report to the Traumatic Shock Committee of the *Medical Research Council* [*see BMB* 92]. This paper, from the Light Department of the *National Physical Laboratory* and the Department of Pathology of *Guy's Hospital*, London, contains the technical details of preparing the new standard in strict conformity with Haldane's original specification (1900–01). New knowledge of hæmoglobin chemistry made it possible for the authors to lessen the possible sources of error in preparing their solution of carboxyhæmoglobin. The solution finally obtained was perfectly clear and has remained unaltered for four years.

As Haldane's method depends on a colour comparison, it seemed better to re-define the standard in terms of colour and to express the tolerances on the same scale.

It is well known that suitable mixtures of the three primary colours can produce any desired colour or tint. The standards necessary for measuring colours in this way were defined in 1931 by the *Commission Internationale de l'Eclairage.* Their reference colours are known as X, Y and

Z. On this system the colour of the standard tubes of carboxyhæmoglobin is expressed by the formula

$$0{\cdot}4805X + 0{\cdot}3432Y + 0{\cdot}1763Z$$

The limits of tolerance are found empirically to be ± 2% in carboxyhæmoglobin concentration.

One advantage in defining the standard in terms of colour is that any tube can be tested as it is and related accurately to the present standard. A suitable correction factor can then be applied to any results obtained with it. For comparisons of this sort the laborious technique used to obtain the colour formula need not be employed. A suitably sensitive optical comparator can be used instead.

An important feature of the specification issued by the British Standards Institution (B.S. 1079 : 1942) is the allowance for variations in tube diameters. In making up their standard solution, manufacturers will in future vary the dilution of the carboxyhæmoglobin solution to suit the diameter of the tube in which it is to be put. A wide tube will be filled with a more dilute solution than a narrow one and *vice versa*. The amount and colour of the light transmitted by the tubes will be the same. Similar variations are permitted in the graduated tubes in which the blood under test is diluted. Thus, although more latitude is allowed in the construction of the instruments, there will be a final gain in accuracy.

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STUDIES ON STORED BLOOD : I. Results in a Series of 427 Transfusions ; II. The Leucocytes in Stored Blood ; III. The Oxygen Capacity of Stored Blood ; IV. Modifications in the Equipment for Blood Transfusion ; V. Observations on the Coagulation Mechanism in Stored Blood ; VI. Changes in the Erythrocytes during Storage ; VII. The Effect of Sodium Sulphapyridine, Albucid Soluble and Hydrogen Ion Concentration on Phagocytosis ; VIII. The Effect of Transfusion on Capillary Resistance ; IX. Further Observations on the Effects of Storage on Erythrocytes ; X. Complement, Iso-Agglutinins and Agglutinogens

by A. Crosbie, J. W. Czekalowski, H. Scarborough, C. P. Stewart & J. C. Thompson, *Edinburgh Medical Journal* [*see references at foot of text*].

A series of papers from the Edinburgh *Emergency Blood Transfusion Service* has appeared since the outbreak of war. Paper I (Stewart, 1940a) deals with the organisation of the Service which was modified and expanded to form a " blood bank." The technical methods and apparatus used are described in this paper and in paper IV (Stewart, 1940b) of the series. A particularly interesting feature is the method of blood withdrawal which ensures that the blood is never in contact with an excess of citrate. The stream of blood from the donor's vein mixes with a stream of 3·8% sodium citrate delivered from a measured container holding 50 cm.^{3} The concentration of citrate in the final mixture (450 cm.^{3}) is approximately 0·38%.

Paper II (Crosbie & Scarborough, 1940) of the series deals with changes in the leucocytes, 50% of which disappear from blood during 4–5 days of storage. This disappearance is not influenced by oxygen saturation or by maintaining or increasing the concentration of glucose. Lymphocytes disappear more slowly than polymorphonuclear neutrophils. Eosinophils and monocytes are intermediate. The motility of leucocytes is unimpaired during the first four days of storage but diminishes after that. It cannot be observed after the sixteenth day.

In paper VII (Czekalowski, 1941) it was shown that the phagocytic index and the percentage of leucocytes taking part in phagocytosis are both increased by sodium sulphapyridine in concentrations ranging from 55·3 to 0·33 mg./litre. This effect was analysed and the authors believe it to be due to a stimulating effect of the drug on leucocytes.

Papers VI (Crosbie & Scarborough, 1941) and IX (Crosbie & Scarborough, 1942a) reported studies on the effect of storage on erythrocytes. Considerable variation was noted between different samples of blood. The rate and degree of disappearance of erythrocytes was found to be dependent on the initial count, the fall in numbers being greater with higher counts. This fall in the erythrocyte count is associated with an increase in the corpuscular volume and thickness. Erythrocytes in various specimens of blood attain the spherical state at approximately the same rate, the time taken varying with the specimen from 3–10 days. The development of spherocytosis is accompanied by an increase in both osmotic and mechanical fragility and spontaneous hæmolysis occurs as early as the tenth day of storage. The erythrocyte sedimentation rate becomes gradually slower as a result of storage. an effect which can be induced in fresh erythrocytes by mixing them with stored plasma.

In paper III (Scarborough & Thompson, 1940) in the series it was shown that neither the hæmoglobin content nor the oxygen-capacity is impaired by storage for periods of up to 30 days.

In paper V (Crosbie, Scarborough & Thompson, 1941) the authors report their observations on the coagulation mechanisms in stored blood. They show that the thrombocytes agglutinate during the first 2–3 days and that their number is greatly reduced after 4–6 days. This disintegration is associated with increased coagulability of the plasma. The coagulation time (Howell) and prothrombin time (Quick) gradually increase, reaching 50% of the initial values in about 35 days. No change in the fibrinogen content of blood was found to occur during 50 days of storage.

In paper VII (Scarborough, 1941) an immediate and remarkable increase in capillary resistance is shown to follow transfusion of blood or plasma (but not saline). This effect has been demonstrated to follow the transfusion of fresh blood, stored blood, and plasma stored for 7 months.

In paper X (Crosbie & Scarborough, 1942b) of this series, the authors report observations on complement, iso-agglutinin and agglutinogen potencies. Hæmolytic Complement activity was assessed in citrated plasma in terms of the greatest dilution at which hæmolysis was observed after incubation at 37° C. for 40 minutes. A 2% suspension of washed erythrocytes in contact with a standard dilution (5 M.H.D.) of amboceptor was used as indicator. The complement titre was found to fall rapidly to 30–50% of its initial value during the first 2–4 days of storage (in contact with cells). The rate of decrease did not appear to be greater when the initial value was high.

The titre of the iso-agglutinins α and β was assessed by the usual technique in terms of the greatest dilution in normal saline at which agglutination could be observed with standard fresh erythrocytes. It was found that the agglutinin titre was maintained for at least 6–8 weeks of storage. After that a slight fall occurred. Agglutinogen potency of stored erythrocytes was assessed in a similar manner against standard high-titre serum. For periods up to 8 weeks the agglutinogen potency was not affected by storage.

In the course of the investigation it was found that blood samples kept at room temperature for short periods (2–7 days) gave a better agglutination reaction when the cells were diluted with 3·8% citrate instead of 0·9% saline. The authors accordingly suggest that 3·8% sodium citrate is to be preferred as a diluent to 0·9% sodium chloride for blood taken for grouping purposes if the tests cannot be performed at once.

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STUDIES ON STORED BLOOD : XI. Phagocytosis in Stored Citrated Blood and the Opsonic Power of Stored Liquid Plasma

by J. W. Czekalowski (Poland), *Edinburgh Medical Journal*, 50, 40–56, January 1943

Although in recent years the value of stored erythrocytes as oxygen carriers, the persistence during storage of the factors concerned in blood coagulation, and the behaviour of the

" defence mechanism " have all been the subject of numerous investigations, the literature on phagocytosis in stored blood, one of the elements of this mechanism, appears to be scanty. The findings of previous investigators as regards the effect of citrate on phagocytosis are conflicting, but Karavanoff (1935) and MacDonald & Stephen (1939) found a rapid decrease in phagocytic power as a result of storage. Kolmer (1939), using citrated (0·35 %) blood, observed that phagocytosis for *staphylococcus aureus*, *streptococcus hæmolyticus* (Group A) and *B. coli* was in some cases slightly reduced after 24 hours' storage, more markedly reduced after 3 days, and disappeared after about 7 days.

The present author, working in the Edinburgh and South-East of Scotland *Emergency Blood Transfusion Service*, found (1942) that with blood stored in 0·38 % sodium citrate, phagocytosis for *streptococcus viridans* (Type R) disappeared between the 6th and 8th days of storage. In the investigation now reported, total leucocyte count, differential count, viability of leucocytes, " index of degeneration " (number of degenerated forms expressed as a percentage of total) were assessed in blood withdrawn from middle-aged Group O donors and stored in 0·38 % sodium citrate at 2·5° C. In a phagocytic system (the standard procedure was to mix equal volumes of the bacterial suspension and the appropriate plasma and incubate at 37° C. for 30 minutes with continuous shaking) containing *S. viridans* (type R) the number of cells taking part in phagocytosis and the mean number of ingested organisms per leucocyte were also determined. Degenerative changes (nuclear deformity and junction karlorrhexis) in the leucocytes were observed after storage for 24 hours to be followed within 72 hours by kariopynosis, kariolysis, cytoplasmic vacuolation, granularity and basophilism. The index of degeneration was found to be 19 % 24 hours after withdrawal, and reached 95 % after storage for 8 days. During the first 3–5 days of storage viability of the leucocytes was well maintained but was absent by about the 14th day. From the very beginning of storage there was a rapid decrease in phagocytic activity until the 3rd or 4th day, and phagocytic activity ceased after 5–8 days of storage. The addition of large amounts of stored plasma to the phagocytic system, or incubation for 60–90 minutes, had very little effect in prolonging phagocytosis.

In these experiments the cells and plasma were stored together for similar periods. The results suggest that the gradual decline in phagocytic activity was due not only to disappearance of viable and morphologically normal leucocytes but also to changes in the plasma. In a second series of experiments the stored cells were incubated with a mixture of bacterial suspension and fresh plasma. It was concluded that, as phagocytosis was now appreciable until the 11th or 12th day of storage, fresh plasma had a stronger opsonic activity than the stored plasma. It was also found that when phagocytosis had ceased in systems containing stored plasma, it could be restored by the addition of fresh plasma.

In a third series of experiments the phagocytic system contained fresh washed cells, bacterial suspension and stored plasma. In such a system phagocytosis remains appreciable for 20 days (instead of 5–6 days with stored cells); but with plasma stored for not more than 4 days there was no definite change in the percentage of cells taking part in phagocytosis.

The author concludes that decrease and final disappearance of phagocytosis from stored blood should be referred not only to degeneration and dissolution of leucocytes but also to the disappearance of certain factors from the plasma. One of these factors is a normal opsonin, but a second is either complement or one of its components or an unknown substance which stimulates opsonisation. The opsonising activity of stored plasma can be increased by the addition of a little fresh plasma to an extent greater than can be accounted for by the opsonising effect of the latter. It is suggested that during opsonisation a compound BO_x is formed between bacteria (B) and opsonin (O), x representing the " degree of opsonisation " and hence the tendency to be ingested. The formation of BO_x is potentiated by a second factor which may be complement or one of its components. Phagocytosis of the opsonised organism requires a " normal " leucocyte and involves a reaction between BO_x and active groups at the cell surface. In a series of systems in which the leucocytes are of constant phagocytic power this theory requires that phagocytosis will be determined by the number of opsonised organisms. Experimental evidence is cited in support of this hypothesis and further experiments to test it are planned.

A practical implication of this study is that blood stored for more than 24 or at the most 48 hours should not be transfused with the object of strengthening the recipient's " defence mechanism " in cases of infection and especially in septicæmias.

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The object of this Bulletin is to provide a guide to medical science and thought in Britain, and it consists mainly of summaries of a representative selection of British papers on subjects of medical interest. Any material appearing in the Bulletin may be published without fee, but acknowledgment of the source, by addition of the initial letters BMB followed by the serial numbers of the items selected, would be appreciated. The Bulletin is not distributed generally to the medical profession.

SPECIAL CONTRIBUTION

MEDICINE AND SPEECH

by DOUGLAS GUTHRIE, M.D., F.R.C.S., Ed.

[*The need for the international exchange of ideas and information is especially evident in the field of medical science, and many medical men find it necessary to acquire a knowledge of other languages in order to maintain contact with advances in their subject.*

In this article, the author reviews some aspects of speech which may be of special interest to the medical man with linguistic inclinations.]

The war has clearly demonstrated that it is the duty of the medical profession to maintain health as well as to treat disease. The scope of medicine is widening. The opinion of the doctor is now sought on matters which were originally outside his sphere. Education, housing, and nutrition claim the attention of every medical man, and he is regarded as the best source of information upon many other matters. Now there is one topic, of interest to everyone, which has not yet received the attention which its importance demands. The science and art of singing and speaking have attracted mankind ever since man acquired that extra function, which differentiates him from the lower animals. During recent years the mechanical reproduction and transmission of the human voice by telephone, gramophone, sound-film and wireless have given a great impetus to the study of speech. Physicists and psychologists have made noteworthy contributions to the subject, but physiologists, and even laryngologists, have neglected it to such a degree that one may search their standard text-books in vain for an account of the normal functions of the organs of speech and voice.

In a short article such as this, one can give only a brief outline of the subject and indicate the sources from which the reader may obtain full information should he desire to pursue the matter further.

Speech Therapy

The medical practitioner naturally approaches the study of speech from the pathological aspect, as he is often consulted on account of disorders of speech. These are fairly common in childhood, and fall into four classes: (1) Deafness, (2) Imperfect articulation, (3) Nasal speech, and (4) Stammering. Let us briefly examine each in turn.

The diagnosis of deafness in infancy is no easy matter. A child is brought for advice, during his second year, because he does not speak, and the doctor must decide whether this is a case of (*a*) deafness, (*b*) mental defect, or (*c*) retarded speech. Much depends upon his verdict, especially if the child is deaf, as it is then essential that education should commence not later than the third year.

The problem of deafness and of the education of the deaf child is the subject of an excellent work by Dr. and Mrs. A. W. Ewing (1938), and there is much interesting information on the physical aspects of hearing in a little book by Beatty (1934) or the larger work by Stevens & Davis (1938).

Imperfect articulation may be due to deafness for high tones. A high pitched consonant such as S is not heard and is therefore not reproduced. In other cases the defect of speech may arise from dental irregularities. Nasal speech is present in cleft palate, as the nasopharynx cannot be closed, and the only sounds correctly articulated are the nasals.

Stammering is the commonest of all speech disorders; about 2% of all school children are affected. It is now generally agreed that stammering, more correctly called stuttering, is of psychogenic origin and demands treatment conducted on psychological lines. A number of recent works deal with the problem of stammering. One of the latest is by Boome & Richardson (1931).

During recent years there has appeared a new type of specialist, the speech therapist, usually a student of drama who has made a special study of speech disorders. Efforts are being made to establish speech therapy on a sound basis and to secure a definite standard of knowledge among those who practise it. Guidance and advice, such as only a medical man can give, are essential to the success of such an enterprise. Speech therapy deserves to be raised to the level of an exact science and this can only be done following the principles of physiology and psychology.

One of the earliest investigators of disorders of speech was Professor John Wyllie of Edinburgh, whose book, although it appeared as long ago as 1894, is still worth reading. In a more recent work, the entire subject of speech in childhood, its development and disorders, is discussed by Seth & Guthrie (1935).

The Organs of Speech and Voice

It is popularly believed that the tongue is the organ of speech and the larynx the organ of voice. The truth is, that those are only parts of the complex mechanism which enables us to speak and to sing. The vocal apparatus consists of three parts, intimately linked together so as to act in unison. The three parts are: the thorax, which supplies the air at requisite pressure; the larynx, which produces the fundamental note of voice; and the mouth and throat, which form the articulate speech.

Respiration

The lungs, evolved for respiration, have become, in the course of further evolution, an integral part of the vocal apparatus. For speech or song a prolonged act of expiration is essential. Expiration is normally a passive movement. During inspiration the thoracic cavity is enlarged, and the lungs in consequence are filled with air, by the elevation of the ribs and by the descent of the diaphragm. The intercostal muscles raise the ribs in bucket-handle fashion and thus expand the chest; the diaphragm, as it contracts, pulls down the floor of the chest, enlarging it in a vertical direction. When those muscles relax their effort, there occurs the phase of expiration, which is simply a passive recoil. Nevertheless, when voice is used, the act of expiration is reinforced by contraction of the abdominal muscles. Every singer practises this method of controlling breathing, and the movements of the chest and abdomen during voice production have been repeatedly studied by the stethograph. There is wide difference of opinion among teachers as to " breath control " and the subject demands further scientific investigation.

Vocalisation

The second component of the vocal apparatus is the larynx. The vocal cords are really not cords nor bands, although they appear so in the laryngoscope. They are the free edges of the crico-thyroid membranes. Subjacent to the " cords " and sharing every movement are the thyro-arytenoid muscles. They are the muscles which give to the cords their rigidity, density, and shape, each quality varying according to the pitch of the note. There are some sixty other laryngeal muscles, all paired, all acting in unison, and all concerned in holding the cords in certain requisite positions. Neither the muscles nor the cords produce the vocal sound; it is the air which is the sounding body. Thus the larynx cannot be compared to a violin or other musical instrument. It resembles a siren in the fact that the sound is caused by a rapid succession of puffs of air; it acts to some extent like a reed, but no reed is capable of adjusting its vibrating edges. The best simile is perhaps that of the lips of a trumpeter.

Vocal cord vibration has been studied by means of the stroboscope. This instrument enables one to view the larynx with a beam of interrupted light. One obtains a composite picture made up of fractions of different vibrations so that the vocal cords seem to be in slow motion. A more accurate view of vocal cord movement has been recently secured by the Bell Telephone Company in America, using cinematography at the very rapid rate of 4,000 frames per second. Pressman (1942) has described this film, which clearly shows how the vocal cords, vibrating with an undulating motion, elongate as the pitch rises. As it rises still further a " damping " effect, akin to the fingering of a violinist, comes into play, and only the anterior part of the cord vibrates.

Much confusion has arisen regarding the " registers " of the voice. It is now recognised that the terms " chest register " and " head register " must not be held to apply to the chest or head. Nevertheless there is a change of

mechanism in singers as the higher notes are reached. What happens during this change is not clearly understood, but it is agreed that the chest does not act as a resonator nor does the palate act as a sounding board.

The comparative anatomy and physiology of the larynx in numerous animals has been studied by Negus (1929), who agrees with Wyllie that the larynx was originally a valve. He also shows how the larynx secures fixation of the thorax while the upper limbs are in use, how it is modified to assist the function of deglutition and olfaction, and how, finally, it came into use as a convenient means of producing sound.

Resonance and Articulation

The third part of the vocal apparatus is formed by the cavities of the throat and mouth which constitute two resonators, each capable of considerable alteration and adjustment, so that a great variety of speech sounds may be produced. The movements of the lips and of the facial muscles and jaws are visible, and therefore available to the " lip reader " ; those of the tongue and palate are naturally less obvious.

A number of ingenious devices have been applied to the investigation of articulate speech. Radiography is naturally useful, although the lateral view shows the speech organs in one plane only. The size and shape of the resonators is of less importance than the extent of the openings between them, and between the mouth resonator and the outer air.

Speech sounds follow each other in such rapid succession that they are not easily recorded. Each sound lasts for $\frac{1}{30}$ to $\frac{1}{10}$ of a second, the ordinary rate of speech being 600 sounds per minute, or about 160 words. In the cathode ray oscillograph we have a very sensitive method of recording speech, a means which has been used by Curry (1940) with interesting results.

Sir Richard Paget (1930) has shown by means of models that each vowel and consonant is characterised by two or more resonances. He believes that all speech arose from signs. The signs, originally made by the hands, were copied by the jaws, tongue, lips, etc., just as a child, while laboriously learning to write, follows the movements with his protruded tongue. All speech sounds, according to Paget, are postures or gestures.

The English Speech-Sounds

In every language there are " vowels " and " consonants." About 50 sounds may be recognised in standard English. There are five vowels in the alphabet, but, as English is by no means phonetic, there are as many as 22 vowel sounds, 12 simple vowels and 10 diphthongs. The varieties of sounds represented by the letter " A " may be appreciated if we note how it is pronounced in such words as *talk* (ɔ:), *tap* (æ), *tape* (ei), and *father* (a:). [The phonetic symbol for each of these sounds is given in parenthesis.] Many years ago Helmholtz showed that vowel sounds were produced by reinforcement of certain overtones or harmonies of the fundamental laryngeal note. Each vowel has its own appropriate pitch, although it may be produced over a long range of notes. It is not easy to sing " oo " (u:) on a high note, nor " ee " (i:) on a low note. The overtones also give to the voice its characteristic quality or timbre.

At one time consonants were regarded as noises, but it has been shown that they are capable of musical analysis, although some, such as S, contain harmonies of very high frequency. The majority of consonants result from complete or partial obstruction to the outgoing current of air at seven different points, with or without vocal sound. Thus they are classified as " plosives " or " stops " (although it is the release and not the stop which produces the consonant), and as " fricatives," when the air is forced through a narrow channel. The fricatives include F, V and Th. The plosives are P, T and K, which when " voiced " become B, D and G. The only English nasal speech sounds are M, N and Ng. W, L, and J in English are regarded as semi-vowels.

The average pitch of speech is 140 vibrations per second in men, and 300 in women, but, as already mentioned, certain consonants have components of much higher frequency. In singing, the human voice ranges over about three octaves, at frequencies (per second) extending from 80 to 1,000, though such average limits are often exceeded. As has been proved by Fletcher (1929), intelligibility is hardly affected by cutting out all frequencies below 500 and above 3,000.

The Development of Speech

Much may be learned from a study of the gradual appearance of speech in the normal child. Many painstaking studies of individual children have been made, and have been collected by Lewis (1936) in a recent work of great interest. The new-born infant cries on a note of 435 per second, and the vocal range extends to an octave by the age of 4 and an octave and a half just before puberty, when the voice is said to " break " into the adult type, falling as much as an octave in pitch in boys. As regards speech, the *oo-eh* cry of discomfort is soon voiced, and some consonant sounds may be noted even in infancy. Smiling and facial gesture, important preliminaries to speech, appear in the 8th week of life. Babbling sounds, which occur even in deaf children, commence in the second month. The infant seems to derive great satisfaction from those sounds, and the babbling stage may continue even after the child uses words. Spoken language is understood some time before it is spontaneously used. The child attaches meaning to a word which is not always correct. and he may " try it out " by giving varied pronunciations. At the early stage he may invent words and talk a gibberish of his own, the " little language " as Jespersen (1922) has called it, which should not be suppressed as it is simply the experimental trial of a new instrument. About the tenth month the first word appears ; thenceforward the vocabulary rapidly increases. An interesting study of the growth of language has been written by Pillsbury & Meader (1928). Additional interest may be added by the perusal of a simple and popular work by Sir James Jeans (1938) which clarifies some difficult problems in acoustics.

Conclusion

While it cannot be claimed that the foregoing statement does more than touch the fringe of a wide subject, it is hoped that the reader's curiosity has been stimulated, and that he may be tempted to continue the study by perusal of some of the sources quoted. The list is by no means complete, but it may easily be extended by the reader himself. With one exception, the references are books and not journals, as papers on speech are widely scattered in many sciences and rather difficult of access. All the works mentioned may be easily obtained and each of them contains numerous other references for the student who wishes to continue his enquiry.

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VITAMIN A AND BONE GROWTH

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THE EFFECT OF BONE DYSPLASIA (OVERGROWTH) ON CRANIAL NERVES IN VITAMIN A-DEFICIENT ANIMALS

by E. Mellanby, *Journal of Physiology*, **101**, 408–431, 25/3/43

[In a series of papers published since 1926 the author, working first at Sheffield University and later in the Nutrition Building of the *National Institute for Medical Research* (London), has shown that degenerative changes in many nerves, both cranial and peripheral, may be produced in young animals by dietetic means. The dietary conditions producing these results are deficiency of vitamin A and carotene, and the presence of a high proportion of cereal. The former of these two factors is the more important since, even if the cereal content of the diet be very high, degeneration will not occur in the presence of sufficient vitamin A and carotene. If, however, potatoes replace cereal, it is difficult to produce the effects of vitamin A deficiency. Although most of the experimental work is concerned with young dogs, similar changes occur in rabbits and in rats. In young animals the degenerative changes in the nervous system become well established in afferent nerve fibres in both central and peri- p systems, but to a much less extent in efferent fibres, riod of about four months. A much longer experi- al period is required to produce any such change in lt animals.

The commonest lesions consist of demyelination followed by complete disappearance of the fibres in many of the afferent cranial and peripheral nerves and ascending fibres in the central nervous system. Degenerative changes in the axis cylinders also occur and may sometimes be found where there is no other obvious defect in the nerve. It has been shown that the nerve cells are also affected. Powdering of the Nissl granules, eccentricity of the nucleus, concentration of glial cells around the nerve cells and even the disappearance of the latter have been described, especially in the posterior root ganglia and corresponding ganglia in the brain, Clarke's column and other posterior horn cells and cells of the dentate nucleus. The author believes that the nerve cell changes may precede the demyelination of the nerve fibres.

These widespread changes in the nervous system are responsible for characteristic alterations in behaviour of young animals which develop deafness, inco-ordination, stiffness and weakness, especially of the hind limbs, cramps and occasionally convulsions. Ataxia and lack of concentration and attention in puppies fed on rachitogenic diets were in fact the original observations from which the subsequent investigations developed. (An account of the author's earlier work is given in his (1934) *Nutrition and Disease*.) The characteristic symptoms of deafness in these animals led to a very complete histological study of the labyrinth capsules of young dogs fed for 4–10 months on diets deficient in vitamin A and carotene but complete in other respects (Mellanby, 1938). Degeneration up to complete disappearance of the cochlear nerve and the cells of the spiral ganglion with their central and peripheral branches and, to a lesser degree, degeneration of the vestibular portion of the 8th nerve, was a constant finding. Serous labyrinthitis with secondary degeneration of the sensory epithelium of the labyrinth developed in the course of time. These changes were found to be due to pressure upon, and stretching of, the nerve fibres as the result of an overgrowth of bone, especially in the modiolus, and of the periosteal layer of the capsule near the brain. Examination of the bone of the skull revealed other bony overgrowths and deformities which suggested that the degenerative disturbances previously noted in other cranial nerves, especially the optic and trigeminal nerves, might be similarly explained.]

In later publications (Mellanby, 1939, 1941), including the present paper, these observations have been extended. Thickening and deformity of the cribriform plate pressing upon the olfactory fibres, and stenosis of the optic foramina compressing the optic nerves are both described. Degenerative changes in the latter nerves, however, are also mediated by increased intracranial pressure, and by a direct degenerative effect of vitamin A deficiency on the retina itself. Deformities of the petrous part of the temporal bone may compress the Gasserian ganglion and this could account for the degenerative changes in the sensory divisions of the Vth nerve. It is suggested that xerophthalmia may be a manifestation of loss of neurotrophic control over the conjunctiva and cornea. While degenerative changes in all the cranial nerves with sensory function have been described, the cranial nerves with motor function can suffer considerable stretching and even compression without degenerating. Overgrowth of the cranial bones may press upon and produce deformity of parts of the brain. The greatest bone overgrowth is found in the posterior fossa, especially around the foramen magnum, and may almost obliterate the cisterna magna. Bone abnormalities have also been found in the vertebral columns, compressing the spinal cord particularly in the cervical region. More definite pressure effects can often be recognised in the posterior root ganglia. The general effect is that, although the bones surrounding the nervous system grow, the space they surround does not expand at the same rate as the central nervous system, so that the latter is compressed.

When the deformities in the skull and vertebral column are considerable there is often evidence of increased intracranial pressure. The pressure of the cerebrospinal fluid in the cisterna magna may be double that found in animals receiving similar diets containing, in addition, vitamin A.

The author concludes from these physiological experiments and histological studies that a function of vitamin A is to influence the structure of growing bones, probably by limiting the number and the degree of activity of osteoblasts and osteoclasts. In its absence from the growing animal, first osteoblastic activity seems to be stimulated and later osteoclastic activity may be increased, thus resulting in proliferation of cancellous at the expense of compact bone, and causing many bones to lose their moulding and outline and to become thickened and enlarged. In all these experiments, where the intake of calcium was not high, the increased bulk of certain bones was due to the formation of an excess of cancellous tissue. This was not observed in the control animals.

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MINERAL METABOLISM

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CALCIUM METABOLISM AND NUTRITION PROBLEMS

by J. D. Robertson, *Nature*, **151**, 379–381, 3/4/43

This paper from the *Courtauld Institute of Biochemistry*, Middlesex Hospital (London), contains the substance of a lecture delivered before the Royal Society of Arts.

The skeleton is the sole calcium store in the body. The calcium in the cortex of the bones is relatively constant and stable, but the calcium in the bony trabeculæ forms a labile endogenous reserve (and is continuously participating in the calcium exchanges in the body) whereby the serum calcium is maintained within the narrow range of 9·9–11·1 mg. per 100 ml., in spite of wide fluctuations in the intake and excretion of calcium.

The chief exogenous sources of calcium are milk, eggs, dairy produce, and green vegetables. Absorption of calcium may be interfered with owing to a high content in the diet of oxalic acid (for example in spinach), of phytic acid (in cereals), or of phosphorus, all of which render a proportion of the calcium unavailable. The presence of free hydrochloric acid in gastric juice and of protein in the diet, and the collateral absorption of fat all tend to promote the absorption of calcium. In infants the ratio of calcium to phosphorus in the diet is of major importance in promoting efficient absorption. The optimal ratio of calcium to phosphorus is 2 : 1. As age increases the maintenance of the ideal ratio is of less importance, provided that the phosphorus does not greatly exceed the calcium. Vitamin D in doses of 700–1000 international units daily aids absorption of calcium from the gut, but very large doses, 50,000–1,000,000 international units, mobilise calcium and promote its excretion.

The calcium metabolism of the body is influenced by the activity of the parathyroid and, to a less extent, the thyroid

gland. Parathyroidectomy results in a fall in blood calcium which is corrected by the administration of parathyroid extracts. In thyrotoxicosis the urinary calcium excretion is increased and in severe cases skeletal decalcification is evident radiologically.

Calcium is excreted in the ratio of 25 % in the urine and 75 % in the fæces. A variable proportion of the latter, however, represents unabsorbed calcium. Calcium is also lost into the fœtal skeleton, two-thirds of which is formed during the last three months of pregnancy, and into the milk of the lactating female. When the intake of calcium is low, the body responds by decreasing excretion. Calcium is, however, never absent from the urine and fæces even on a calcium-free diet, and during pregnancy and lactation as much calcium is excreted as normally.

Although some individuals may achieve equilibrium between intake and output on a daily intake of 200 mg., the optimal calcium intake is greater since it has been shown that higher intakes benefit growth, weight, fitness, health, and material efficiency in both animals and man. As the result of studies on the calcium balances of normal healthy people the optimal amounts of calcium that should be ingested daily to promote ideal health are believed by nutritional experts to be the following: adults, not less than 800 mg. daily; children, not less than 1000 mg. daily, and pregnant and lactating women, about 2000 mg. daily. Severe calcium deficiency may be detected by clinical examination—softening and bending of the bones, brittleness of the bones, pathological fractures, and tetany—and these conditions have been reported in Great Britain as a result of a low calcium intake by Maxwell (1934) and, more recently, by Anderson & Brown (1941). Radiographic examination of the skeleton is a somewhat more sensitive indication of calcium deficiency and such evidence has been obtained in this country by Owen, Irving & Lyall (1940). A different method of approach is that of the mass dietary survey; Orr (1936) estimated that approximately twenty-two million people in the lower income-groups in Britain were not getting sufficient calcium. A fourth method of investigation is by calcium balance determinations. Such evidence of calcium deficiency also exists in Britain (Owen, Irving & Lyall, 1940; Harris, Ireland & James, 1941).

Under war conditions the supply of calcium-rich foods is limited, and it is probable that the consumption of the non-priority classes of the population is sub-optimal. The requirements of the priority classes (children under five, and pregnant and lactating women) are probably satisfied by the allowance of one pint [about 570 cm^3.] of milk per day and 4 ounces [about 112 g.] of cheese per week (≡ 800 mg. Ca per day). The position is greatly improved by the addition of calcium to bread, a practice which was established in Mexico and Peru when Columbus discovered America, and which was employed in Germany in 1914–18. The amount of chalk added now to 280 pounds [about 128 kg.] of flour is 7 ounces [about 200 g.]. If the average daily intake of bread per person is 14 ounces the average extra consumption of calcium is less than 200 mg. daily. This is about the amount that is consumed daily in the hard-water districts of Britain where the water contains 12 mg. Ca per pint [about 570 cm^3.]. There is no evidence that this is deleterious; in fact these districts include many of the health resorts of the country.

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[*For the effects of phytic acid in cereals on mineral metabolism, see BMB* **14** & **15**]

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THE EFFECT OF PROTEIN INTAKE ON THE ABSORPTION OF CALCIUM AND MAGNESIUM

by R. A. McCance, E. M. Widdowson and H. Lehmann, *Biochemical Journal*, 36, 686–691, September, 1942

Lehmann & Pollak (1942) observed that phosphates and carbonates of Ca and Mg were much more soluble in solutions of amino acids than they were in water. They therefore suggested that amino acids might facilitate the absorption of Ca. To prove or disprove this hypothesis the present authors, of the Department of Medicine, Cambridge University, decided to study in human subjects the effect of varying protein consumption upon the absorption and excretion of Ca and Mg.

Five human subjects were used, four men and one woman, and each carried out two experiments. One experiment was carried out at a high level and one at a low level of protein intake. As far as possible the calcium, magnesium and phosphorus intakes were made equal in each set of two experiments. The experimental organisation and all technical details have previously been described by McCance & Widdowson (1942).

The authors found that increasing the amount of protein in the diet raised the amount of Ca and Mg absorbed from the gut and subsequently excreted in the urine. They point out that this result explains anomalies in earlier experiments by other workers, *e.g.* Mellanby (1921) found in his studies of canine rickets that lean meat had a definite anti-rachitic effect. Mellanby (1925) also found that dried milk had some anti-rachitic effect apart from the calcium it contained.

The present authors draw attention to the fact that meat is a poor source of calcium, but it may so promote the absorption of calcium by providing a plentiful supply of amino acids that it becomes the equivalent of a food rich in this mineral. This explains why Eskimos, who are largely carnivorous and whose calcium intakes cannot be large, tend to be well grown and have good teeth, and it provides an additional reason for recommending high protein diets in pregnancy and lactation.

The experiments also gave evidence that protein facilitates the absorption of phosphorus but that this effect is small.

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FOOD TABLES: Their Scope and Limitations

E. M. Widdowson & R. A. McCance, *Lancet*, **1**, 230–232, 20/2/43

In this paper from the Department of Medicine, Cambridge, the authors, who are themselves well known as the compilers of a most comprehensive manual on *The Chemical Composition of Foods* (McCance & Widdowson, 1940), point out that there are two schools of thought about tables of food values. One regards them as figures of undisputed accuracy, and the other regards them as valueless because the composition of foodstuffs may be so profoundly modified by the soil, season, or rate of growth. It is suggested that the truth lies somewhere between these two views.

The authors discuss experiments, which have been carried out in different parts of the world, to discover whether the nutritive value of diets, as calculated from tables of figures, differed significantly from the values as obtained by direct analysis of the food eaten. They point out that disagreements have arisen when the diet of one person over a period of less than one week is compared by this method. On the other hand, when results for a number of persons or for a single person over a period of several weeks are compared, the agreement is very much better.

A comparison of figures obtained by the authors over a number of years has shown fairly good agreement between figures obtained by analysis and those calculated from the authors' own tables, except in the case of calcium and iron. The discrepancy in the iron figure was probably due to the fact that curried fish figured prominently on the menus employed, as curry powder is known to have a large and variable amount of iron in it. The discrepancy in the calcium figure was due to the fact that no allowance was made for the calcium obtained from the tap water used in cooking and making tea.

The authors point out that the iron values given in food

tables should always be taken as minimum values. Some of the reasons for this are that the cutting of foods, particularly fruit, with kitchen knives, cooking in chipped enamel pots, and the use of an iron mincer, add appreciably to the amount of iron in food. The following table illustrates the importance of this factor.

	Iron mg./100 g.
Apples cut up with stainless steel knife and cooked in distilled water in glass beaker . . .	0·31
Apples cut with ordinary kitchen knife and cooked in distilled water in glass beaker . . .	2·30
Apples cut up with ordinary kitchen knife and cooked in distilled water in chipped enamel pan	6·00

It is clear that stewed apple prepared in the third fashion becomes as good a source of iron as the best roast beef, and 100 g. of it, which is quite a moderate helping, would provide half the daily requirement of iron. Similarly beef as purchased contained 2·73 mg. of iron per 100 g., while after passage through an iron mincing machine it contained 4·79 mg. per 100 g.

A similar "contamination" by calcium occurs in the cooking of vegetables, and up to 200 mg. of calcium per day may be obtained from drinking water in districts where the water is very hard. This is as much as there is in the British adult milk ration (about 1140 cm^3. per week) during the winter months. The use of hard water and of salt considerably increases the calcium content of vegetables as shown below.

Vehicle in which Boiled	*Calcium mg./100 g.* *Potatoes*	*Peas*
Distilled water	4·71	22·4
Cambridge tap water (hard) . .	6·69	38·9
Cambridge tap water with kitchen salt	9·28	44·9

The kitchen salt used contained 0·329 % calcium. The authors conclude that the extra calcium acquired by culinary "contamination" is very small in quantity (4–7 mg. daily) compared with the amount obtained from hard drinking water (estimated at 60 mg. daily in the authors' area).

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PHYSICAL FITNESS, HYPERTHYROIDISM AND HÆMORRHAGE

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VITAMINS AND PHYSICAL FITNESS

by A. A. Harper, I. F. S. Mackay, H. S. Raper, & G. L. Camm, *British Medical Journal*, **1**, 243–245, 27/2/43

This paper from the Departments of Physiology and Mathematics of Manchester University reports an experiment carried out to test whether fitness of University students has diminished since the beginning of the war, as a result of a deficiency in the average student's diet.

Procedure of Experiment

Two groups of students were taken, and the diet of one group was supplemented with vitamins. Bases of comparison of the two groups were—anthropometric data, "physical fitness tests," and incidence of minor ailments.

Sixty-nine subjects of similar age and social background were used. They lived in University halls and had ordinary undergraduate diets. The experiment lasted for 21 weeks.

In addition to the usual anthropometric data subjects were examined as follows:

(*a*) heart-rate (resting, standing, and with exercise),
(*b*) resting vital capacity, post-exercise vital capacity,
(*c*) the R.A.F. breath-holding and endurance tests.

The following vitamin supplements were given daily to one group (*I*): 6,000 units vitamin A; 1,000 units vitamin D; 50 mg. vitamin C. The control group (II) received daily capsules of arachis oil and tablets containing citric acid, identical in appearance with those given to group I but devoid of vitamins.

Each subject was interviewed fortnightly, and any complaints during the preceding 2 weeks were noted, especially those of respiratory infections, gastro-intestinal disturbances, and bleeding from the gums. At the end of 10 weeks all subjects were re-examined and the groups were transposed. Final examination occurred after a further 11 weeks. Each subject had the same examiner on each occasion and neither examiner nor subject knew whether the latter had received control or vitamin tablets.

Results

(i) Minor complaints: Incidence was 50 % greater in the control group. The mean figures (in days of minor illness per man) were: vitamin group, 9·7 days; control group, 14·9 days.
The mean difference was $5·2 \pm 1·7$.

(ii) Physical examinations:
Anthropometric measurements showed no significant difference between the groups, and there was no significant difference in the standing and post-exercise heart rate or in the post-exercise vital capacity. The mean resting vital capacity was the same for both groups at the beginning. At the second examination there was an increase in both groups which was greater in the vitamin group. The third examination showed an increase in the vitamin group and a decrease in the control. The findings for breath-holding time in seconds resembled those for vital capacity. In the endurance test (maintenance of a column of mercury at 40 mm. by steady expiration), the vitamin group each time showed a greater increase.

The results of these experiments suggest that even during the summer months the diet of the students examined was sufficiently below the optimum level in respect of vitamins A, C and D to produce a significantly greater amount of minor respiratory and gastro-intestinal affections than a similar diet supplemented with these vitamins. The greater improvement in resting vital capacity and in breath-holding and endurance times in subjects receiving vitamin supplements may be a reflection of this lessened susceptibility to minor infections, or may be due to some other action of the vitamins.

The validity of these conclusions may be attacked on two grounds: first, that the number of subjects (69) was too small for an experiment upon nutrition and physical fitness; and secondly, that the differences between vitamin and control groups in vital capacity *etc.*, are not striking enough to warrant the drawing of any conclusions. These differences are, however, greater than those found by Jokl *et al.* (1941) in repeated examinations of a small group of subjects, and the homogeneity of the group of men examined for the present experiment offsets to some extent the objection to the small number used.

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EFFECT OF VITAMINS ON EXPERIMENTAL HYPERTHYROIDISM

by V. Korenchevsky, K. Hall, & B. Clapham, *British Medical Journal*, **1**, 245–247, 27/2/43

In hyperthyroidism the metabolism of the body is stimulated and food constituents are oxidised more readily. Therefore there is an increased demand for vitamins. Failure on the part of workers to realise the antagonistic effects between thyroid hormone and certain vitamins makes it difficult to draw definite conclusions from their work.

The experiments reported in this paper from the *Lister Institute*, London, were undertaken because the problem of the relationship between thyroid hormones and vitamins is of great importance for the proper therapeutic application of these substances in several diseases, for the treatment of hyperthyroidism, and also because of the confusion about the subject which exists in the literature. In the first series of experiments non-toxic doses of thyroid hormone and of vitamins were used. Experiments were performed on 121 male rats for investigation of the effects of vitamins B and C, and on 66 female rats for vitamins A and D. The ages of the rats averaged 150 days. Each experiment was repeated twice.

In the first experiment (on male rats), 85 mg. of desiccated

thyroid were given orally three times a week and 0·6 mg. of thyroxine was injected subcutaneously twice a week. In the second experiment (on female rats) 180 mg. of thyroid were given orally 6 times a week for the first month, and 280 mg. at the same intervals for the second month.

The doses of vitamins for the first experiment were as follows:

Vitamin A: 1,300 international units 6 times a week
„ D: 70 „ „ 6 „ „
Aneurin: 0·22–0·5 mg. per day
Riboflavin: 0·22–0·5 „ „

In the second experiment the same doses of the B vitamins were given orally, but in addition the following doses of vitamins were injected 6 times a week:

Aneurin: 0·4–0·5 mg.
Pyridoxine: 0·5 mg.
Calcium pantothenate: 1·5–2·0 mg.

In both experiments 20 mg. of vitamin C were given orally by pipette 3–6 times a week, and in addition 25–40 mg. were injected subcutaneously 6 times a week. The duration of the first series of experiments was 53 days and of the second 47 days.

Estimation of the relative effects of the hormone and the vitamins was obtained by weighing a number of organs and the whole animal at the conclusion of the experiment. The organs weighed were: testes, seminal vesicles, prostate, penis, adrenals, thyroids, thymus, liver, kidneys, spleen, heart, abdominal fat.

An additional experiment was performed on 18 male rats in order to discover in particular whether different effects were produced by the thyroid hormone and vitamins B when toxic doses of thyroid hormone were given (*i.e.* 1 mg. of thyroxine injected daily for 13 days). The rats were killed on the 14th day of the experiment. The same amounts of the same vitamins B were given as in the previous experiment except that the dose of aneurin injected was raised to 1 mg.

The experiment showed that in addition to the well-established katabolic properties of thyroid hormone in raising body metabolism and reducing body fat, it possesses also some anabolic properties which can lead to "better development" in liver, kidneys, spleen, heart, and adrenals in both sexes, and in ovaries in females.

In female rats it was found possible to reduce the body fat to about one-fifth of its normal value without appreciably affecting the gain in body weight. This was presumably due to increase in the weight of other organs.

Such useful effects of the thyroid hormone are prevented unless liberal amounts of vitamins are also given, because of the increased requirements of vitamins.

These findings suggest that the best therapeutic results can be expected from the simultaneous administration of vitamins with thyroid hormone. There is no indication of direct antagonism between any vitamins and the thyroid hormone.

The original paper contains tables showing the mean weights of the organs and whole bodies in the different groups of rats tested.

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THE VITAMINS IN RELATION TO HÆMORRHAGE
by H. Scarborough, *Edinburgh Medical Journal*, 50, 85–119, February 1943

This paper from the Clinical Laboratory of the *Royal Infirmary*, Edinburgh, is a review of the subject but contains much original material; it is documented by detailed descriptions of twelve typical cases.

The mechanisms which exist for the control of hæmostasis are described in some detail, and attention is drawn to the complex and little understood relationship between the various parts of the complicated biological pattern. The author suggests that in some hæmorrhagic conditions the fault may lie in a disturbed relationship between parts of the complex, rather than in the break-down of a single process. The sole precipitating cause for bleeding is trauma, the word being extended to include the physiological stresses and strains of muscular activity and the erect posture. Hæmostasis occurs as the result of a defect in the body's mechanisms for the arrest of bleeding. Excessive or abnormal bleeding may be produced by excessive or unusual forms of injury, even when the hæmostasis mechanisms are intact, and cases are described illustrating these points. The bleeding diseases occur as the result of single or multiple defects in the hæmostasis mechanisms, but again the bleeding is initiated by trauma. The methods used in the investigation of the illustrative cases are described, and the author passes to a consideration of the part played by vitamins in the hæmorrhagic diseases.

In 15 cases of thrombocytopenic purpura, ascorbic acid, either by mouth or intravenously, was of no value in increasing either the thrombocyte count or the capillary resistance. Vitamin A by mouth and parenterally was likewise ineffective, as was also vitamin P and a diet containing a high proportion of fresh vegetables and fruit. Ascorbic acid and preparations of vitamin P introduced directly into the bone marrow were also ineffective. In one case, suggestive evidence in support of vitamin T (the thrombocyte factor of Schiff & Hirschberger, 1937) was obtained. The position in respect of vitamin K and the hæmorrhagic tendency in certain cases of jaundice is reviewed. The author does not consider that hypoprothrombinæmia is an important factor in contributing to the bleeding tendency in cases of hepatic cirrhosis in which a capillary defect (low capillary resistance) is found. There is a positive correlation in cases of hepatic disease between the capillary resistance and the bleeding time, especially if the latter be determined by the method of Ivy, Shapiro & Melnick (1935). In certain jaundiced subjects the increased bleeding time can be reduced by the parenteral administration of vitamin D. The author believes that in hepatic disease a low capillary resistance plays an important part in mediating the bleeding tendency, and throughout the paper the importance of capillary as distinct from hæmatological factors is stressed.

Further evidence is given in support of the idea that at least two forms of hæmorrhagic disorder may follow nutritional deficiency in man. Scurvy is cured immediately by administration of ascorbic acid, but the capillary resistance is not necessarily low in scurvy, is not the main factor responsible for the bleeding, and is not controlled by ascorbic acid. A second hæmorrhagic disorder characterised by a low capillary resistance, prolonged bleeding time, low serum calcium, and the development of petechial bleeding in dependent parts, is due to vitamin P deficiency and is resolved by administration of this vitamin. Because scurvy is a multiple deficiency disease, and because vitamins C and P occur together in their natural sources, these two conditions are frequently found associated. A case is described in which the syndrome of vitamin P deficiency occurred, during the daily administration of ascorbic acid, in a subject where scurvy had been resolved by vitamin C. It was finally cured by the administration of vitamin P preparations. The difference between these two hæmorrhagic disorders is described in detail, and it is finally suggested that vitamin P might play a part in the treatment of certain vascular (non-thrombocytopenic) purpuras. The evidence in favour of this statement, however, is at present tenuous.

In referring to the nature of vitamin P, the author recommends that statements that it is identical with the flavanone hesperidin should be accepted with reserve. Extracts many times more potent, weight for weight, than hesperidin have been prepared from black currants and tested in guinea-pigs (Bacharach & Coates, 1942) and in man (unpublished observations by the present author).

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VITAMINS AND ORAL HYGIENE

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NUTRITIONAL AND OTHER FACTORS IN "TRENCH MOUTH," WITH SPECIAL REFERENCE TO THE NICOTINIC ACID COMPONENT OF THE VITAMIN B_2 COMPLEX
by J. D. King, *British Dental Journal*, 74, 113–122, 141–147 & 169–176, 5 3 43, 19 3 43 & 2 4 43

Following the successful treatment (King, 1941) of a [illegible] cases of Vincent's disease (trench mouth, ulcerative [illegible]

stomatitis) the author, who is at present seconded from the British Army Dental Service to the *Medical Research Council*, undertook a large-scale investigation, the results of which are reported in this paper. The clinical material was as follows :

Treatment by nicotinic acid (internally) .	81 subjects
„ „ chromic acid, hydrogen peroxide, scaling, etc. (locally) .	60 „
„ „ combined nicotinic acid and local measures . . .	121 „
„ „ ascorbic acid (vitamin C) internally and hydrogen peroxide locally . . .	14 „
Examination and diagnosis only of trench mouth cases . . .	150 „
„ of fit personnel for fuso-spirochætal microflora . .	100 „
„ of part of a military unit three months after the reported end of an outbreak of trench mouth	125 „
Total . . .	651 subjects

The subjects were all connected with the British Army. ong the 431 positive cases of trench mouth were 10 officers ; other ranks ; 8 members of the ATS (the women's liary service of the Army) ; 2 officers' wives ; 2 privates' ves (one six months pregnant) ; and one private's daughter (aged six years). Excluding the child, the average age was 25 years, with extremes of 18 and 45 years. Diagnoses were made from clinical signs and symptoms and microscopic examination of direct films from the gums and other tissues of the mouth and throat. Dental conditions were recorded in detail and particular attention was also given to general signs and symptoms such as anorexia, lassitude, malaise and mental inertia.

For purposes of diagnosis and prognosis, the lesions were divided into three types or phases :

Type I. Acute fulminating : Very rapid onset ; characteristic fœtor ; pseudo-membranous ulceration of gums, especially in interdental and lower retromolar regions, which may extend to lips, cheeks, palate, tongue (more rarely), fauces, tonsils, etc. ; regional adenitis ; malaise, lassitude, drowsiness, mental inertia, anorexia, and sometimes slight rise in body temperature ; food debris about the teeth, but little or no calculus and mouth generally well cared for. Incidence comparatively low ; sporadic occurrence in spring and summer months.

Type II. Sub-acute : Insidious onset ; patient usually aware of little but a vague feeling of discomfort or intermittent bleeding and soreness of gums, which may be accentuated by unaccustomed heavy physical exertion or exposure to damp and cold ; little or no fœtor ; gums often bright red in colour but may have a purplish or greyish tinge if complicated by chronic parodontal disease ; interdental papillæ and/or third molar flaps congested, swollen, blunted and often detached at their summits ; no definite ulceration ; calculus deposits and general condition of mouth show evidence of neglect ; few or no systemic disturbances apparent ; spontaneous recovery may occasionally occur but usually an exacerbation into true ulceration results if tissue resistance becomes further depressed. Incidence probably comparatively high throughout year, but lesions often unrecognised.

Type III. "Flaring" sub-acute : Insidious onset with sudden exacerbation into true ulceration. Signs and symptoms then closely simulate those of Type I, but there is a history of former subacute disease of some long standing, or of previous ulcerative lesions ; calculus deposits are present and there are obvious evidences of oral neglect. Incidence relatively high in autumn and winter months.

Details of treatment were as follows :

(*a*) **Nicotinic acid :** 150–200 mg. daily by mouth during treatment, followed by maintenance dosage of 100 mg. daily for 7–14 days.

(*b*) **Ascorbic acid :** 200 mg. daily for duration of treatment.

(*c*) **Local hygienic therapy :** Chromic acid (20%) applied to all gums and other affected tissues, followed immediately by vigorous rinsing with hydrogen peroxide at first visit ; scaling and same treatment on second day ; atomising with hydrogen peroxide on 3rd, 4th and 6th days. Peroxide mouthwash in morning, evening and after each meal.

(*d*) **Combined nicotinic acid and local therapy :** Nicotinic acid 150 mg. daily, and chromic acid (reduced concentration of 10%), scaling and hydrogen peroxide, syringeing and mouthwash as for (*c*).

Results of the various forms of treatment are shown in the table below. The sporadic comparatively infrequent

Type of case	*Treatment*	*No. of cases* *	*Average time for clinical healing of lesions (days)*
I Early Summer	(1) nicotinic acid	28 (12)	5 (extreme, 10 days)
	(2) local	20 (8)	4 (extreme, 10 days)
	(3) nicotinic acid + local	20 (2)	2 (extreme, 4 days)
	(4) ascorbic acid + H_2O_2	10 (8)†	no response up to 14th day
II Throughout year	(1) nicotinic acid	21 (4)	9 (extreme, 12 days)
	(2) local	10	6 (extreme, 11 days)
	(3) nicotinic acid + local	21	2 (extreme, 4 days)
	(4) ascorbic acid + H_2O_2	4 (2)	no response up to 14th day
III Autumn Winter	(1) nicotinic acid (a)	22 (9)	10 (extreme, 16 days)
	(b)	10 (2)	unsatisfactory response
	(2) local	30 (8)	7 (extreme, 15 days)
	(3) nicotinic acid + local	80 (10)	2 (extreme, 4 days)
	(4) ascorbic acid + H_2O_2	—	—

* Figures in brackets in column 3 indicate number of cases treated in hospital.

† Six of the ascorbic acid cases were subsequently treated with nicotinic acid and all responded satisfactorily.

Type I lesions responded fairly rapidly to nicotinic acid alone ; cases of the subacute (Type II) and "flaring" subacute (Type III) types were less satisfactory, but nevertheless usually reacted (more slowly) to the vitamin. Of the ten cases which failed to respond, all were of the "flaring" subacute variety. The most effective method of treatment tested was in the form of combined nicotinic acid and local hygienic therapy. With this technique, the lesions of all types responded within four days, as compared with ten to fifteen days for local treatment alone ; liability to relapse was also considerably reduced. No satisfactory response could be obtained in the 14 cases treated by ascorbic acid (vitamin C) and hydrogen peroxide.

In a study of the signs and symptoms of trench mouth and the constitutional and local conditions which accompany it, the author noted that general lowered tissue resistance and local oral traumatism were by far the most frequent predisposing, contributory or associated clinical factors. Of the constitutional factors, infections such as the common cold were the most prominent.

The author believes that the prevalence of the common cold and allied infections during the autumn and winter months is directly related to the incidence of trench mouth which, in Britain at least, also reaches its peak during this period of the year. Other indications that depressed tissue resistance was concerned were provided by the observed adverse effects of heavy or unaccustomed physical exertion, exposure to cold and damp, and by the symptoms of malaise, lassitude, mental inertia and anorexia, which so often accompany the disease. It is probable that such conditions increase the amount of tissue respiration factors (*e.g.*, nicotinic acid) needed for the welfare of the tissues. If the increased requirements are not available, a relative deficiency may be induced in the presence of a dietary intake believed to be adequate under more normal circumstances. Local conditions associated with the onset of trench mouth were found to include all those which assist in the establishment of a more or less chronic gingivitis. Their rôle appears to be mainly traumatic, using this term in its widest sense, and may account for the absence of the disease in edentulous mouths.

The significance of the fusiform bacillus and spirochæte of Vincent in the lesions of trench mouth was studied (i) by

microscopic examination of more than 2,000 direct smears from subjects affected by both ulcerative and non-ulcerative gingivitis, and (ii) by the experimental induction of ulcerative gingivo-stomatitis in the author's own mouth. In addition, cultivation of the organisms was carried out in a few cases. One hundred soldiers rendered " dentally fit for war service " were examined for incidence of gum lesions in relation to fuso-spirochætal mouth flora. Relatively large numbers of both fusiform bacilli and spirochætes were found in 84% of the mouths and in only 5% was there apparently complete freedom from the organisms. In 10% of mouths many fusiform bacilli were present with no accompanying spirochætes, and in the remaining one case spirochætes alone occurred in large numbers. Clinically, 44% had moderately severe marginal gingivitis, the remainder showing little or no evidence of gum disease ; no gum ulceration was found in any of these men. Both micro-organisms were more abundant in regions where gingivitis and calculus existed. These findings were in agreement with those obtained by previous workers (McKinstry, 1918 ; Semple, Price-Jones & Digby, 1919 ; Tunnicliff, 1939), and strongly suggest that the presence of fuso-spirochætal organisms in the mouth is by no means a specific indication of trench mouth. However, in the first 200 cases of the present series, progress of treatment and clinical " cure " were checked by the examination of mouth smears. It was noted that in most cases of the acute fulminating type, treatment by nicotinic acid alone or by the combined method resulted in the disappearance of the fuso-spirochætal combination a few days after clinical recovery. On the other hand, more than two-thirds of the Type III and all of the Type II cases showed a variable number of fusiform bacilli and spirochætes some time after clinical recovery.

In contrast to his previously unsuccessful attempt (King, 1940), the author here describes the induction of ulcerative gingivo-stomatitis in his own mouth by the experimental inoculation of ulcerative debris from a case of Type III. Characteristic signs and symptoms, constitutional and local, were noted and the lesions responded dramatically to the combined nicotinic acid and local therapy. Photomicrographs were taken of biopsy material removed during the peak phase. On the basis of this and the previously reported experiment, no definite conclusions could be drawn. However, in the first and unsuccessful attempt, the author's general and local oral health were good. In the second experiment, severe colds may have lowered his resistance. At the same time food stagnation about the teeth, due to purposely neglected dental hygiene, as well as cervical caries, causing persistent irritation of the gum margin, undoubtedly provided suitable traumatic foci. It may also be of significance that, in contrast to the previous experience, the second and successful induction of the disease occurred at a time following eighteen months of food rationing when, among other things, there was a decreased supply of meat and other foodstuffs containing nicotinic acid and its fellow members of the vitamin B_2 complex. Contact with other cases was carefully excluded during the experimental period.

The author discusses his findings in relation to those of other workers in different fields and refers to the possible influence of certain streptococci and herpetic viruses on the development and progress of the lesions. Factors in the ætiology of the disease are dealt with at some length, but the general conclusions, admittedly of a tentative nature, are summed up as follows :

" Development of the ulcerative lesions described here appears to depend on at least three and possibly four factors, all of which must exist simultaneously or within a relatively short time of one another. It is believed that these factors are : (*a*) chronic traumatic injury of the gums and associated tissues ; (*b*) lowered resistance to disease of the body as a whole ; (*c*) deficiency of nicotinic acid and perhaps of other vitamins ; and (*d*) the action of certain micro-organisms of a specific or non-specific nature."

With regard to the *treatment* of trench mouth a scheme is outlined which is based on the combined nicotinic acid and local hygienic therapy already described. Emphasis is laid on the stimulation of tissue resistance and the elimination of all traumatic foci in the mouth. The same principles are suggested for the *prevention* of the disease and for the control of any apparent outbreaks, bearing in mind that further investigations may disclose other at present unknown factors. Finally, the author concludes :

" At the present time it would be inadvisable to condemn the segregation of trench mouth patients and their feeding utensils where large groups of people are living and feeding communally. It is suggested, however, that when, under these conditions, a few cases of the disease are reported, examination and *prophylactic gum treatment* of as many as possible of that community would do far more to prevent any spread of the disease, especially during the autumn and winter months. At the same time a careful inquiry into the diet *as consumed* and the nutritional status of the community as a whole should be made."

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SORE AND BLEEDING GUMS IN NAVAL PERSONNEL: Vitamin C and Nicotinic Acid Intakes

by C. C. Ungley & J. S. F. Horton, *Lancet*, **1**, 397-399, 27/3/43

This investigation forms part of an enquiry into the cause of sore and bleeding gums in naval personnel noted in 1940 and suspected on clinical grounds alone to be due to vitamin C deficiency. The investigation included a search for clinical and other evidence of nutritional deficiency ; clinical and bacteriological examination of mouth and throat ; estimation of vitamin C intake ; vitamin C saturation tests ; and finally, controlled therapeutic tests.

The men who were admitted to hospital with this gum condition included 38 from mine-sweepers and other small ships, 2 from larger ships and 11 from shore establishments. Men in small ships were seldom at sea longer than three weeks and were usually in port every day or few days. They received the standard ration and a messing or victualling allowance, but did not appear to deny themselves foods containing vitamin C for the sake of mess savings. Together with the men from the larger ships and the shore establishment, their average vitamin C intake varied between 16 and 80 mg. Low levels of intake were sometimes related to food fads.

The main source of vitamin C was potatoes. In some ships freshly cooked potatoes were available twice daily. The average serving was 8 ounces (about 227 g.). Greens were cooked unconservatively and were often kept hot. Dislike of cabbage was common. Vegetables in soups were cooked for many hours—not just added before serving. Most of the other foods did not contribute very much vitamin C to the diet.

Patients were described as saturated, nearly saturated, or unsaturated to varying degrees, according to whether an excretion of 100 mg. or more was obtained after the 1st, 2nd, 3rd, 4th, 5th or 6th test dose of 700 mg. of ascorbic acid. The patients received a diet low in ascorbic acid during and before the tests, but were not as a group any more unsaturated than healthy trawler crews in the same port, or healthy civilians and naval personnel tested simultaneously by McNee & Reid (1942).

Although some cases had been labelled scurvy, none had hæmorrhages into the skin or mucuous membranes other than the gums, and there was no follicular hyperkeratosis. Fatigue and malaise were infrequent and vitamin C had no apparent effect on the feeling of well-being. Appetite was seldom impaired. Two patients with Vincent's infection had excoriation at the angles of the mouth, but there were no other signs suggestive of ariboflavinosis.

Capillary resistance tests by a positive pressure method gave normal results in 49 cases tested. No one complained of defective night vision. In 26 cases the hæmoglobin ranged from 82 % to 120 %. Erythrocytes varied from 4·32 to 5·98 million and the white blood cells from 7·5 to 13·6 thousand per mm.^{3} The differential leucocyte counts were not remarkable. Vincent's organisms were found in the gum smears of all but one patient. In 32 out of 51 patients the clinical and bacteriological evidence of ulcero-membranous stomatitis (Vincent's infection) was clear.

In only three cases did appearances recall the classical picture of scorbutic gums. One improved slightly after ascorbic acid, and two were unaffected. All three cleared up after local treatment.

Ascorbic acid (300 to 700 mg. per day) was given without local measures to 13 patients of whom 9 had ulcero-membranous stomatitis. Improvement was slight in one case

and moderate in two others. The remaining ten patients showed no improvement. Ascorbic acid and other vitamin supplements did not appear to enhance or accelerate the response to local measures.

There was no evidence from this work that the men were suffering from vitamin C deficiency judged by the usual standards. There were only four men whose daily intake of vitamin C was assessed as low as 16 to 19 mg. per day, and most of the diets were estimated to provide more than double this amount. On the other hand the men were certainly not saturated, but there was no indication that subsistence at this intermediate level predisposed to gingival disease.

The alleged relationship between Vincent's stomatitis and nicotinic acid deficiency (King, 1940) was also considered, but (*a*) the cases occurred in a community where pellagra was unknown, (*b*) the dietary intake of nicotinic acid did not appear low, (*c*) there was no evidence of impaired absorption of nicotinic acid nor indication of incipient pellagra, (*d*) 500 mg. of nicotinic acid daily without local treatment caused no improvement in eight cases of gingivitis, of which six had typical ulcero-membranous stomatitis. No relationship between Vincent's stomatitis and nicotinic acid could therefore be demonstrated in this series.

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his paper is reviewed in BMB **34**]

VITAMIN C REQUIREMENTS

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VITAMIN-C INTAKES AT A RESIDENTIAL HOME

by L. J. Harris & M. Olliver, *Lancet*, **1**, 454–457, 10/4/43

The League of Nations (1938) has recommended that the intake of vitamin C should be 30 mg. per day, but in wartime the amount of vitamin C consumed by many people is liable to fall well below this figure. The authors believed that since information on the vitamin C status of the British population in war time is meagre, accurate information on this subject would be supplied by determining the daily consumptions of vitamin C at different seasons of the year in a typical well-conducted institution. By this means it was also hoped to ascertain which common foodstuffs furnished the more important supplies of vitamin C in actual domestic practice.

The investigation was made at a Cambridge home for homeless boys, of whom there were 36 in residence. Their ages ranged from 8 to 14. A daily record was kept of the diet, of the methods of cooking, and of the sizes of portions served. Allowances were made for absentees, illness or similar irregularities. At frequent intervals sample dishes as served were analysed for vitamin C by titration against 2,6-dichlorphenol-indophenol. Bread, cereals, fish and meat were not analysed because their contribution of vitamin C to the diet is nil. The significant sources of vitamin C were potatoes, green vegetables, root crops, fruit in season, and jam. Analysis of the same dish day after day was found to be unnecessary.

Since the exact conditions of cooking and preparation of food were known and standardised, it was possible to base the calculation of vitamin C content of the various foods, as cooked, on the figures given in tables prepared by Olliver (1943). These tables were derived from the results of several thousand estimations over the past seven years.

This investigation showed that the vitamin C intake varied with the season. It was greatest in late summer (50–60 mg. per day) and fell during autumn and winter. It was lowest during March and April (less than 20 mg. per day). The principal cause of the higher intake in the summer was the change from old to new potatoes. This may make as much as 30 mg. a day difference in the vitamin C intake. Another factor in the summer increase was the consumption of home grown cabbage, cauliflower and spinach.

The authors point out that potatoes constitute one of the most reliable sources of vitamin C because they are served regularly with meals. Green vegetables are richer in vitamin C but are not served so often or in such quantities. They believe the consumption of more greenstuffs is to be encouraged, and they feel that good domestic management should be able, by the use of greens, potatoes, and vegetable cooking water (which contains an appreciable amount of vitamin C), to provide a diet, even in winter and spring, which is not seriously below the League of Nations requirement.

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VITAMIN C SATURATION TEST: Standardisation Measurements at Graded Levels of Intake

By L. J. Harris, *Lancet*, **1**, 515–517, 24/4/43

Preliminary data have already been published (Harris, 1942) in support of the finding that various levels of past intake are correlated with the corresponding graded responses to test doses of vitamin C. In the present paper from the *Dunn Nutritional Laboratories*, Cambridge, further data are presented.

The technique of test-dosing used to determine the time taken for the body to become saturated with vitamin C [using approximately 11 mg. per kg. body weight] was the same as that used and described by Harris & Abbasy (1937).

The main human material consisted of about 36 boys in a residential home, but at the same time some incidental comparisons were instituted with working-class boys on poorer but less accurately known intakes of vitamin C, and on research workers, medical students, and women undergraduates. During the four months preceding the saturation tests the diet of the boys in the institution provided them with 20–25 mg. vitamin C per day. One group was kept on this basal diet alone. A second group was given a daily supplement of 15 mg., so that their total intake was 35–40 mg. per day. A third group was given a supplement of 25 mg., so that their daily intake was 40–50 mg. In some tests done in the previous year (1941) the daily intake of vitamin C in the basal diet was 40–50 mg., hence in the two supplemented groups the total amounts received daily were 55–65 and 70–80 mg. respectively.

The results of these experiments are summarised in the following table:

GRADED RESPONSES WITH VARIOUS GRADED PAST INTAKES. SUMMARY

Date of test	Previous intake mg. per day Av. (and limits)	Total boys in group	No. of boys approaching saturation on (days)					
			1st	2nd	3rd	4th	5th	6th
Autumn 1941	75 (70–80)	12	12	0	0	0	0	0
	60 (55–65)	10	10	0	0	0	0	0
	45 (40–50)	10	9	1	0	0	0	0
April 1942	47 (45–50)	12	12	0	0	0	0	0
	37 (35–40)	11	5	6	0	0	0	0
	23 (20–25)	12	0	5	7	0	0	0
Spring 1941	Various poor working-class children. War time diets. Mostly less than 20 mg.	29	1	4	8	11	3	2
Spring 1938	Working-class pre-war, for comparison	35	10	11	9	5		0

As a standard of reference in assessing the results of nutrition surveys it is noted that an intake of about 30 mg., or an amount not seriously in excess of it, suffices in virtually all subjects to give responses by the second day of dosing. The number of days beyond the second may be taken as an index of the relative deficit in the past intake. With intakes of 50–75 mg. per day (the optimal standard recommended by some American authorities) saturation is attained. The saturation test does not pre-suppose that saturation is necessarily physiologically desirable. "Substandard" is not

synonymous with " clinically deficient " and there are degrees of partial deficiency between optimum nutrition and frank avitaminosis.

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[*For a critique of the Vitamin C Saturation Test see BMB* 35]

PREGNANCY AND INFANCY

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DIET IN PREGNANCY

by W. C. W. Nixon, *Journal of Obstetrics and Gynæcology of the British Empire*, 49, 614–636, December 1942

The paper here summarised was delivered as a William Blair Bell Memorial Lecture at the *Royal College of Obstetricians and Gynæcologists*, London.

In 1935 the Technical Commission of the League of Nations published its report on physiological bases of nutrition. This showed that malnutrition was world-wide in its distribution. Nutrition no longer remains a problem in which only the individual or family group takes a live interest. Diet has become one of the most important aspects of public health, and nutrition has become a social obligation equal in importance to sanitation, education and the relief of destitution.

An example of the effect of diet on health can be seen in the diseases which afflict the East African tribes, the Masai and Kikuyu. In the latter who eat largely cereals there is more bronchitis, tropical ulcer and malaria than in the former, who live on meat, milk and raw blood.

Pregnancy is a " diet efficiency " test, and during this physiological strain, border-line states of nutrition will be revealed. The author, who was formerly Professor of Obstetrics at Hong Kong University, has seen Chinese women who, early in pregnancy, appeared quite normal but later showed beriberi (avitaminosis B_1) as pregnancy advanced. A pregnant woman will suffer from night-blindness (due to vitamin A deficiency) before her non-pregnant sister. The effects of drain upon the maternal calcium are seen in the form of osteomalacia. The babies of women suffering from this disease are themselves rachitic. During the last trimester of pregnancy the following percentages of fœtal birth weight are deposited: protein 75 %, fat 93 %, calcium 65 %, phosphorus 68 %, iron 80 %, total birth weight 70 %. It is known that it is in the last trimester that most of the tragic complications arise.

The ideal diet during pregnancy is well summarised by Mellanby (1933). It should consist of 2 pints of milk daily, 1 to 2 eggs or egg-yolk daily, 1 to 2 substantial servings of green vegetable (cabbage, spinach, lettuce) daily, orange or some fresh fruit daily, calf's liver once a week, sea fish twice or more a week, cod-liver oil 2 teaspoons daily. Similar recommendations have been made by McCance (1938) and Orr (1940).

The author has investigated (Nixon, Wright & Fieller, 1942) the amount of vitamin B_1 excreted by women suffering from œdema, high blood pressure, pre-eclampsia and eclampsia. In this series there were 60 abnormal and 46 normal (control) pregnancies. It was in eclampsia (8 cases) that statistical examination of the data showed an excretion of vitamin B_1 significantly below that of the normal control pregnant women. In this investigation, 24 placentæ of normal women were examined and the average content of vitamin B_1 was found to be the equivalent of 19 international units per 100 g. (the average weight of the placenta was 520 g.). The vitamin B_1 content of the placentæ of the eclamptic patients was significantly low compared with the normal. [*But the results of a recent investigation, shortly to be reported in BMB, are against the therapeutic use of vitamin B_1 in toxæmias of pregnancy.*]

The author maintains that the supervision of diet should be one of the primary functions of all those working in maternity and child-welfare clinics. He suggests that there should be Food Advice Bureaux in these clinics, where a demonstrator should discuss with the women what foodstuffs to buy and how they should be prepared for the table. Such a Bureau has been started at the *Soho Hospital for Women*, London, and it has already proved very popular among the patients.

The author concludes with a plea that modern knowledge of nutritional requirements should be put more into practice. Doctors and nurses in hospitals should receive more instruction in practical dietetics, and good food must not be spoiled in the kitchen. He asserts that there would be no need for vitamin capsules from the laboratory if the produce from the land were properly prepared and cooked.

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VITAMIN K REQUIREMENTS OF THE NEW-BORN

by M. Toohey, *Archives of Disease in Childhood*, **17**, 187–197, December 1942

The author points out that it is now established that there is an appreciable drop in the prothrombin levels of new-born infants. The value reaches a minimum figure between the second and fourth days *post-partum* and then rises rapidly until by the seventh day it is nearly normal. Administration of vitamin K is known to prevent this fall. In the investigation reported in this paper an attempt was made to find the required dose of a vitamin K analogue which would prevent any fall in the prothrombin level, and the time of administration to produce the full effect.

The plasma method for estimating the prothrombin level in adults is not suitable for use on infants because it involves repeated venepuncture, and the following method was therefore employed:

Dale and Laidlaw's coagulation tubes were half-filled with an active thromboplastin solution, either brain extract or viper venom. The infant's warmed heel was pricked and the tube was completely filled with blood by capillary attraction, thus giving equal quantities of thromboplastin solution and blood. The remainder of the test is practically identical with the ordinary coagulation time method of Dale and Laidlaw. The filled tube is immediately immersed in water at approximately 100° F. [38° C.], the ends being firmly closed by forefinger and thumb. The tube is rotated till the bead inside the tube stops, denoting that clotting has occurred. The time from the filling of the tube with blood to the bead stopping is accurately taken by a stop-watch. This is the prothrombin clotting time. The whole procedure takes less than a minute to perform and can be easily repeated two or three times on each infant. The end-point is sharp and can be accurately timed.

Using this technique on forty normal infants it was found that the results were comparable with those previously obtained by Toohey (1941) by means of the plasma method of Owen & Toohey (1941).

For the investigation recorded in this paper 98 new-born infants were divided into four groups containing (*1*) 29, (*2*) 24, (*3*) 17, and (*4*) 28 infants respectively.

Doses of synthetic vitamin K, 2-methyl-1:4 naphthoquinone (" kapilon," Glaxo), were given as follows:

Group 1. Mother, 50 mg. before delivery.
Infant, 3 mg. 6–10 hours after birth.

Group 2. Mother, 20 mg. before delivery.
Infant, 10 mg. 4–8 hours after birth.

Group 3. Mother, 20 mg. before delivery.
Infant, 5 mg. 4–6 hours after birth.

Group 4. Infant, 10 mg. 5–8 hours after birth.

The best results were obtained from Group 3. It was found that in this group the doses of vitamin K analogue given were sufficient, not only to prevent any fall in the prothrombin level, but to raise it almost to adult control levels. A single dose of 10 mg. of vitamin K analogue to the infant (Group 4) was entirely effective in preventing any appreciable fall in prothrombin concentration.

The author does not think it necessary to give vitamin K analogue to mothers during the last days of pregnancy. The

vitamin is effective if given during labour and at least 2 hours before delivery.

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SHORTER NOTICES

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AN EVACUATION UNIT FOR DIABETIC CHILDREN

An interesting aspect of the evacuation of school children from the County of London and contiguous areas in 1939 was the special provision made by the *London County Council* for diabetic children under hospital supervision in matters of insulin dosage and dietary, etc. Realising the danger to health which lack of such supervision would involve, the authorities made arrangements to place all diabetic children whose parents desired to take advantage of the scheme under the care of a specially trained staff at the Hutton L.C.C. Residential School in Essex. The initial staff included two medical officers, a dietician, trained nurses, and certain other non-technical helpers, but when the organisation of the diabetic work was complete, the unit was left in charge of the sister-dietician, and the services of medical officers were retained for visiting purposes only. The school, built on the cottage principle, with each cottage self-contained as regards sleeping, dining, and cooking ties, is provided with a chapel, a swimming bath, and adequate space. An average of 50 diabetic children have been g together in two of the cottages since the inception of the and, while the primary purpose of safeguarding health appears to have been amply fulfilled, these children have been enabled to work and play with normal children, and have not been regarded as chronic invalids. The experience gained through this pioneer unit suggests that in post-war planning of state education, the permanent provision of residential accommodation for diabetic children, preferably associated with a school for normal children, should be seriously considered.

(Cairney, H. G., Stewart, M., & Smith, H. (1943), *Medical Officer*, 69, 61)

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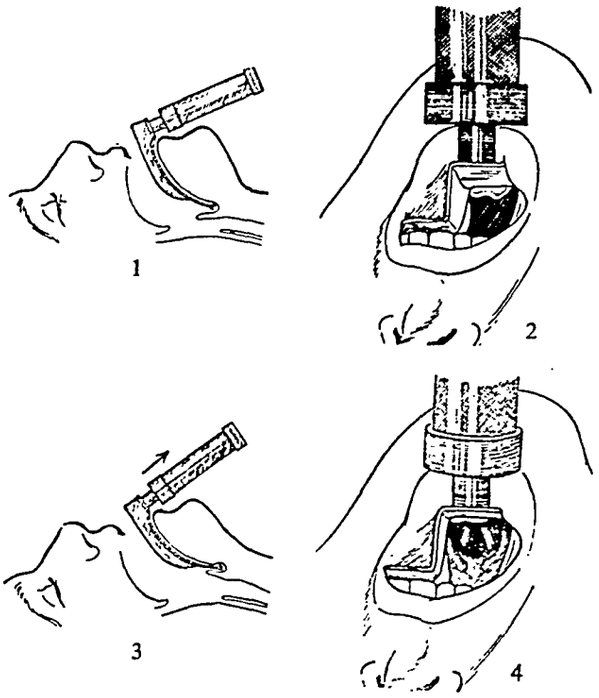
A NEW LARYNGOSCOPE

A recent number of the *Lancet* (13/2/43, p. 205) contains a description of an interesting new laryngoscope designed by Professor R. R. Macintosh, of the *Nuffield Department of Anæsthetics* at Oxford, to lessen the difficulty of exposing the larynx for the passage of an endotracheal catheter. When the short curved blade of this laryngoscope is in position, the tip fits into the angle made by the epiglottis with the base of the tongue (*fig.* 1). The direct view of the epiglottis is shown in *fig.* 2. If the laryngoscope is now lifted (*fig.* 3), the base of the tongue is pushed upwards, and with it the epiglottis, so that the larynx is clearly exposed (*fig.* 4).



FIGS. 1 & 2—SITE OF BLADE AND VIEW OBTAINED BEFORE LIFTING LARYNGOSCOPE

FIGS. 3 & 4—SITE OF BLADE AND VIEW OBTAINED WHEN LARYNGOSCOPE IS LIFTED IN DIRECTION OF ARROW

Reproduced by courtesy of the Lancet

A further advantage is that this instrument may be used at a lighter plane of anæsthesia, without eliciting laryngeal spasm, than any of the standard laryngoscopes, possibly because the blade comes into contact, not with the back surface of the epiglottis innervated by the superior laryngeal nerve, but with the base of the tongue innervated by the glosso-pharyngeal nerve. When not in use the blade unit is folded on the handle, and is easily removed for sterilising.

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BRITISH MEDICAL BULLETIN

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The object of this Bulletin is to provide a guide to medical science and thought in Britain, and it consists mainly of summaries of a representative selection of British papers on subjects of medical interest. Any material appearing in the Bulletin may be published without fee, but acknowledgment of the source, by addition of the initial letters BMB followed by the serial numbers of the items selected, would be appreciated.

PERIPHERAL NERVES

SPECIAL CONTRIBUTION

SPECIAL CONTRIBUTION

RECENT WORK ON PERIPHERAL NERVE INJURIES

by PROFESSOR H. J. SEDDON, D.M., F.R.C.S.

Although the peripheral nervous system has excited the constant interest of many experimental workers and a few neurologists, the clinical problems presented by nerve injuries have not received great attention except during times of war. This is due to the fact that the injuries of warfare involve peripheral nerves with a frequency far greater than that found in the injuries of civil life. Yet in this age of increasing mechanisation, with its toll of accidents which resemble more and more the injuries of warfare, the frequency, and, therefore, the importance of nerve injuries in civil practice, will almost certainly increase. Thus, there is much to be said for maintaining in peace-time the interest and perhaps, in some measure, the clinical organisations that have been engendered by the war. Indeed, the volume of routine work that has to be done in war-time is, to some extent, a hindrance to the pursuit of clinical research in a field where the work is notoriously time-consuming. The answers to many of the questions that now confront us can hardly be sought until those interested are freed from the mass of curative work that now occupies most of their time.

Early in 1940, the British Ministry of Health and the *Medical Research Council* (and later the Department of Health in Scotland), profiting from lessons learned during the last war, set about organising five Centres for the treatment of peripheral nerve injuries, three in England, and two in Scotland. The centres have been established at civilian hospitals in the *Emergency Medical Service* (Ministry of Health), and at each of these, certain members of the staff have made it their business to devote much of their time to the investigation and treatment of nerve injuries and, as the work has increased, to building up clinical teams. By arrangement between the Ministry of Health and the Fighting Services, all Army and R.A.F. cases of nerve injury are directed to one or other of the centres. Civilians eligible for admission to an *Emergency Medical Service* hospital are also provided for, and the result is that a high degree of segregation has been achieved.

The expenses incidental to this work come under four headings:

(i) *Cost of Maintenance of the Patient in Hospital.* This is borne by the Ministry of Health in precisely the same way as applies in the case of other Service casualties, pensioners, and civilian war casualties.

(ii) *Payment of Staff.* At certain centres some or all of the workers are full-time salaried officers in the *Emergency Medical Service.* In some cases, the *Medical Research Council* has provided the salaries of research workers and grants for expenses.

(iii) *Secretarial Staff.* The clerical work is exceedingly heavy, and receives the financial support of the Ministry of Health. The notes are often lengthy and have to be kept in triplicate, so that copies are available for the interested Government departments. In addition, there is a great volume of correspondence with the Ministry of Pensions, and with local hospitals where patients receive treatment after leaving hospital.

(iv) *Patients' Expenses.* Perhaps the most noteworthy feature of the organisation is the provision made for regular follow-up examination. So that patients may suffer no hardship, free travelling warrants are provided whenever their attendance for re-examination is requested; and in certain circumstances compensation is made for loss of wages during the day or two when the man is away from work. As a measure of economy the patient attends the centre nearest to his home, and if this happens to be a centre other than the one at which he was first treated, a copy of the notes is sent to the surgeon who becomes responsible for the follow-up examinations. The only flaw in the scheme is the absence of any provision in cases where the injury is not attributable to the war. A man in the fighting services who is the victim of an ordinary accident while on leave is at present eligible neither for a pension nor for the benefits that make regular follow-up examination feasible.

Until recently there was no provision in the Fighting Services for the systematic treatment of nerve injuries; indeed, it was considered undesirable, since most of the patients would require treatment over a long period, and many would inevitably be discharged as unfit for further service. However, the accumulation in South Africa of numbers of casualties from the Middle East required a special remedy, and a Nerve Injuries Centre has recently been established at a military hospital in Natal; others have been organised in India and the Middle East.

This segregation of patients allows rehabilitation to be arranged in a way that is specially adapted to the disabilities which result from injuries to main nerve trunks. At Oxford, a convalescent centre with 70 beds has been established at a large house about five miles from the hospital.

Rehabilitation takes two forms: (*a*) *General*—physical training, games, orderly duties, lectures and entertainments—such activities as are required to keep men fit mentally and physically; and (*b*) *Specific*—remedial work designed to encourage fine co-ordinated movements of the hands and the improvement of tactile discrimination. This work includes weaving, basket making, toy making, clay modelling and carpentry. A patient recovering from paralysis of the ulnar nerve needs, above all, to develop good control of the intrinsic muscles of the fingers, while one recovering from median palsy must be taught to make the best possible use of such cutaneous sensibility as returns to the thumb, index and middle fingers.

It is often possible for a man to return to work, or even to military service, long before recovery is complete. Over-stretching of paralysed muscles can be prevented by the application of splints designed to protect muscles without limiting movement. In the Fighting Services, this early return to work is made possible chiefly by the increasing specialisation in methods of warfare, and by the readiness of the Services to find work suited to a man's inclinations and physical capacity. As soon as an R.A.F. pilot with external popliteal paralysis has regained full passive movement in the joints of his foot, and has been fitted with a toe-raising spring, he may return to flying—sometimes operational flying—without waiting for recovery in the anterior tibial and peroneal muscles. The same is true of patients with ulnar paralysis. These men continue with their treatment while on active service, care being taken to post them to a station near to a hospital where treatment is available.

Ultimately, some patients make such excellent recovery (mostly radial nerve injuries) that they can be placed in a high category: an enthusiastic young corporal, who had had a tendon transplantation performed because of irreparable damage to the radial nerve, recently wrote from North Africa: "My job during the whole advance was driving a five-ton armoured car, in which I had plenty of exciting moments. I have avenged the wound I received at Dunkirk."

However, such complete restoration of function occurs in only a minority of cases, and many men must leave the Services and return to civil life. It is remarkable how many are able to go back to their old employment; if training in a new occupation is required, the Ministry of Labour takes care of them, and the Government training schemes, started two years ago, are now working well.

In the war of 1914–18, the organised treatment of nerve injuries was due to the efforts of Major-General Sir Robert Jones, Inspector of Military Orthopædics. At his instigation, cases were segregated at a number of centres, and several of them were placed under the care of orthopædic surgeons. It seemed to him that as nerve injuries were frequently associated with injuries to bones, joints, tendons and muscles, the work could best be done by men specially interested in the surgery of the limbs, that is, orthopædic surgeons. This arrangement, peculiar to the United Kingdom, has to some extent been followed in the present war, and at three of the centres the Directors are orthopædic surgeons. There are undoubted merits in the plan, but the responsible surgeon must either take the trouble to become a neurologist himself, so far as the peripheral nervous system is concerned, or he must work in close collaboration with a neurologist. However, the interest and ability of the man are of far greater importance than his professional designation, and the arrangement made at any one centre depends primarily on the local talent available. There is much to be said for the surgeon who is prepared to immerse himself in the minutiæ of neurological diagnosis, for his approach to a case will then be more enlightened than that of the surgeon who is little more than a technician, exploring a nerve under the direction of the neurologist.

Research may be considered under three headings:

(i) *Documentation and Analysis of Clinical Material.* This not only provides a necessary check on the efficacy of various forms of treatment but may lead to the clearer definition of various types of nerve injuries. A preliminary note (Seddon, 1942) has already been published on a classification of nerve injuries which covers the majority of lesions encountered in clinical practice. This classification is now being worked out in greater detail especially in regard to partial lesions. Elkington (1942) has published a short account of nerve injuries produced by the injection of drugs of the sulphonamide group. Other work is now in progress on the classification of nerve injuries due to traction, to ischæmia, and to compression of nerves by sub-fascial effusions (Parkes, unpublished work at the Glasgow Centre).

(ii) *Special Methods of Examination.* It is often possible, by the employment of such methods, to obtain from patients information of a kind that would be difficult or impossible to elicit by other means. Highet (1943) has shown that in three cases out of four, one or more of the thenar muscles are innervated by the ulnar nerve. By blocking nerve trunks with a local anæsthetic (1942) he has shown how anomalous cutaneous or motor innervation may be elucidated; by employing a simplified electromyograph, Weddell, Feinstein & Pattle (1943) have provided an easy means for determining whether a muscle is normally innervated, partially innervated, denervated, or completely destroyed; and Richards at Edinburgh [unpublished work] is using skin temperature measurements as an index of vasomotor disturbances resulting from nerve injury.

(iii) *Animal Experiment.* Lastly, animal experiment may be employed to determine the precise nature of the changes in nerve and muscle consequent on various kinds of nerve injury.

It is only by a balanced combination of clinical observation and animal experiment, however, that steady progress can be made. On the one hand, animal experiment permits the observer to examine his material in elaborate detail; on the other, certain observations can be made only on subjects who can describe their experiences with some accuracy—the investigation of cutaneous sensibility has been almost entirely dependent on the services of the human volunteer. Hence, it is important that laboratory and clinical investigators should work together or, at least, examine each other's work fairly frequently. Laboratory experiment may explain the shortcomings of a generally accepted operative procedure—for example, the work of Highet, Holmes & Sanders (1943) on the deleterious effect of post-operative stretching on nerves, after extensive resection and suture. By contrast, a laboratory technique, ideal in animal experiments, may prove of only limited value in clinical practice; for example, fibrin suture of nerves (Seddon & Medawar, 1942). Precise methods for working out the rates of regeneration of nerves were elaborated experimentally in animals (Gutmann, Guttmann, Medawar & Young, 1942); these, in turn, led to the development of a method for working out rates of regeneration in man (Seddon, Medawar & Smith, 1943), which revealed something that had not been shown in the animal experiments, namely, that the rates of regeneration are not uniform—they fall off as the process approaches completion.

This local co-ordination of the work of the clinician and the experimental biologist has been expanded to cover the work at all five centres.

The Peripheral Nerve Injuries Committee of the *Medical Research Council* meets regularly under the chairmanship of Brigadier George Riddoch, a pupil of Henry Head; he is Consulting Neurologist to the Army, and Consultant Adviser on Nerve Injuries to the Ministry of Health. It is the business of this Committee, not only to stimulate research and to survey progress, but to see that there is no unnecessary duplication of effort. There is also a liaison with the Neurological and Neurosurgical Committees of the *National Research Council* of the United States, helped by a free interchange of bulletins describing the work being done at centres in both countries.

In this way, knowledge is slowly but surely being accumulated, and put to use in practice. The clinical records are kept in such a way that after the war a *corpus* of detailed information will be available for analysis. Between 3,000 and 4,000 patients have already been treated at the Centres; ultimately, this great and constantly increasing mass of material should provide a very complete picture of this fascinating field of neurology.

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[1] [*See BMB* 134] [2] [*See BMB* 115] [3] [*See BMB* 114] [4] [*See BMB* 127] [5] [*See BMB* 128]
[6] [*See BMB* 113] [7] [*See BMB* 118] [8] [*See BMB* 142]

Professor H. J. Seddon has occupied the Chair of Orthopædic Surgery at Oxford since January, 1940. He is Clinical Director of the Wingfield-Morris Hospital and of the Nerve Injuries Centre that has been established there. Nearly 1,000 patients have passed through this Centre since July 1940, and most of them are still under observation.

The experimental work at Oxford is carried out, for the most part, in the Department of Zoology and Comparative Anatomy. All the workers, headed by Dr. J. Z. Young, are biologists. Yet they frequently work in the hospital, and the clinicians in the laboratory. The Centre as a whole provides a good example of the benefits that derive from the joining of forces of a purely scientific with those of a clinical department.

[*In the article on pages 74–75, the organisation and methods adopted in Britain for the segregation and study of peripheral nerve injuries are outlined. The rest of this issue is devoted to reviews of recent published work on this subject, most of which has been carried out at the Oxford Nerve Injuries Centre and in the University Scientific Departments at Oxford and Birmingham. Special acknowledgment is due to one of the Oxford workers, F. K. Sanders, for having contributed the majority of the abstracts published below.*]

DIAGNOSIS AND THERAPEUTICAL PROCEDURES

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A CLASSIFICATION OF NERVE INJURIES

by H. J. Seddon, *British Medical Journal*, **2**, 237–239, 29/8/42

British neurologists normally recognize three fundamental types of nerve injury, namely nerve "contusion," "compression," and "concussion." However, while these terms hint at the cause of injury, they do not describe the actual effect of the injury on the nerve itself. In this paper the author, who is Nuffield Professor of Orthopædic Surgery at Oxford, proposes a classification of nerve injuries in terms which are descriptive of the lesions themselves. Nerve injuries are divided into three classes, namely:

(i) *Neurotmesis*, in which the nerve has been completely divided, and a complete sensory and motor paralysis develops, from which recovery cannot take place spontaneously.

(ii) *Axonotmesis*, in which the nerve fibres are damaged to such an extent that complete peripheral degeneration occurs, but the perineurium and the more intimate supporting structures of the nerve remain in continuity, and spontaneous recovery by regeneration can occur. The clinical signs, however, are still those of complete paralysis.

(iii) *Neurapraxia*, used to describe paralyses so short-lived that recovery from them cannot possibly be due to regeneration. Paralysis in this type is rarely complete, and its clinical characteristics are:

(*a*) the paralysis is predominantly motor;
(*b*) there is little muscle wasting or loss of electrical reactions;
(*c*) subjective sensory disturbances, such as tingling, numbness, burning, are common;
(*d*) objective evidence of disturbances of sensibility to touch, pain, cold, or warmth is rare;
(*e*) there is often a loss of postural or vibration sense;
(*f*) there is rarely any loss of sweating.

The classification is based on a study of 460 cases at the Oxford Peripheral Nerve Injury Centre. Obviously, all cases of peripheral nerve injury cannot be classified under these three simple headings. Injury frequently affects different parts of the nerve, or different fibres, to varying degrees, and the clinical picture is thus often complex. However, all cases can be effectively described by combinations of two or three of the types defined above.

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PROCAINE NERVE BLOCK IN THE INVESTIGATION OF PERIPHERAL NERVE INJURIES

by W. B. Highet, *Journal of Neurology and Psychiatry*, **5**, 101–129, July & October 1942

This paper from the Nuffield Department of Orthopædic Surgery, Oxford, illustrates the value of peripheral nerve block as a diagnostic procedure in cases of peripheral nerve injury. The author describes a technique by means of which any nerve may be located and anæsthetised for a period of from one to three hours. This is done in the following way: A hypodermic syringe containing the solution (2% procaine with 0·002% adrenalin) used to anæsthetise the nerve, is attached to a fine needle, electrically insulated by means of a phenyl resin except for 1 or 2 mm. at its tip, and connected to one pole of a faradic coil. The other pole leads to a broad moist plate applied to some neutral area such as the back of the thigh. When the current is turned on and the needle inserted, its tip acts as a unipolar stimulating electrode, and as soon as the nerve is touched the patient experiences a tingling sensation over the peripheral distribution of the nerve. When the nerve has been found in this way, the anæsthetic is injected either intraneurally (2 cm.^{3}) or else around the nerve (5–10 cm.^{3}).

Nerve block by procaine is regarded as complete when the following conditions are observed: (*a*) vasodilation, anhidrosis, and analgesia throughout the autonomous zone of the skin area supplied by the nerve; (*b*) complete and lasting paralysis of muscles supplied by the nerve distal to the site of block.

This method has been found useful by the author as a means of investigating (i) anomalous innervation of muscles, (ii) supplementary and trick movements, (iii) sensory and sudomotor distribution of peripheral nerves, in relation to the differentiation of complete and incomplete or recovering lesions, (iv) the vasomotor distribution of peripheral nerves.

The usefulness of nerve block in these various connections is demonstrated by reference to 13 cases treated by the author.

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INNERVATION AND FUNCTION OF THE THENAR MUSCLES

by W. B. Highet, *Lancet*, **1**, 227–230, 20/2/43

According to the classical description, the thenar muscles fall into two groups: (1) those lying superficial to the tendon of *flexor pollicis longus* and innervated by the median nerve, and (2) those lying deep to this tendon, which are innervated by the ulnar nerve. Many authors, however, have pointed out that considerable variations in the nerve supply of these muscles exist (*see* Foerster, 1929).

The present author has analysed 20 cases of median nerve paralysis at the Wingfield-Morris Orthopædic Hospital, Oxford, by direct stimulation of the nerves through the skin, and by means of the technique of procaine nerve block which he describes elsewhere (Highet, 1942). In 16 cases *flexor pollicis brevis* was active; in 4 cases there was action in *opponens pollicis* in addition; and in 2 cases *abductor pollicis brevis* also participated in the action. All of these muscles are normally innervated by the median nerve, so in 16 out of 20 cases the innervation of the thenar muscles was anomalous. In all of them the anomalous innervation came from the ulnar nerve.

The author points out that it is important to realise that anomalous innervation of these muscles frequently occurs, as faulty diagnosis of an incomplete or recovering lesion has been made in many cases of complete division of the median nerve because of good action in one or more of the thenar muscles. This has led to an unnecessary delay in the performance of nerve suture.

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116

SPLINTAGE OF PERIPHERAL NERVE INJURIES

by W. B. Highet, *Lancet*, **1**, 555–558, 9/5/42

In this paper from the Wingfield-Morris Orthopædic Hospital, the author describes the general principles of peripheral nerve injury splintage and the types of splint in use at the Oxford Peripheral Nerve Injury Centre.

The following are the principles which must be observed in correct splintage of nerve injuries:

(1) *Avoidance of stretching* of paralysed muscles either by gravity or the action of antagonists. The paralysed muscles must be splinted so that their points of origin are approximated to their points of insertion.

(2) *Avoidance of immobilisation.* All joints of the paralysed limb must be allowed as full a range of movement as is compatible with the relaxation of paralysed muscles. Continual immobilisation of joints leads to stiffness and permanent disability.

(3) *Avoidance of pressure.* The splint must not press on an analgesic area of skin or interfere with the circulation.

(4) *Occupational therapy.* Splints must be such that the

patient can return to work, or carry out occupational therapy, while still wearing them.

All splints must be removed for half an hour twice every day, when physiotherapy is carried out and each joint of the limb put through its full range of passive movement. Although this involves the transient stretching of paralysed muscles, the result is probably not harmful.

At the Oxford Centre the following types of splint are employed:

(i) For *median* palsy. An elastic splint is used to hold the thumb in a position of palmar adduction and opposition. This is necessary to prevent adduction contracture of the thumb.

(ii) For *ulnar* palsy. A 'knuckle-duster' splint is employed, which holds the fingers in slight flexion at the metacarpo-phalangeal joints, and prevents stretching of the *interossei* and *lumbricales*. The splint also prevents the development of a claw hand, since, when the fingers are in slight flexion, the *extensor communis digitorum* can extend the interphalangeal joints.

(iii) For *radial* palsy. An elastic extension splint is employed, similar to that recommended by the *Medical Research Council* after the last War. In this palsy the fingers must never be immobilised, and a fixed full-length splint which places the wrist joint in full extension should be avoided.

(iv) For *circumflex* and *brachial plexus* palsy. An abduction splint is used with a universal joint in the elbow part. This avoids the stiffness of the shoulder and elbow which follows the use of a fixed splint.

(v) For *sciatic* palsy. Side-irons, hinged at the ankle, and a toe-raising spring are used.

In conclusion the author states that splints should be applied as soon as possible after injury, but that improper splintage is worse than no splintage at all.

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FIBRIN SUTURE OF PERIPHERAL NERVES

by J. Z. Young & P. B. Medawar, *Lancet*, **2**, 126–128, 3/8/40

Suture of peripheral nerves by stitches, even if these are restricted as far as possible to the epineurium, produces considerable disorganisation of the regenerating nerve fibres. In this paper from the Department of Zoology and Comparative Anatomy, Oxford, the authors describe how the cut stumps may be stuck together by means of a concentrated plasma gel. The stumps are held together, and concentrated plasma freshly mixed with a strong tissue extract is poured round them. In about ½–2 minutes the plasma clots to a firm jelly which adheres to the nerves and holds the stumps together. The gel remains long enough to allow a firm union to be established between the divided ends.

The concentrated plasma was prepared from cockerel blood. This is withdrawn from the carotid artery (about 100–150 cm.^{3} could be obtained from a single bird) through oiled cannulæ into large centrifuge tubes. These are packed in ice for 10 minutes and then centrifuged, after which the supernatant plasma can be easily separated. From part of this plasma the fibrinogen is precipitated. One volume of blood is mixed with 9 volumes of redistilled water, and then with 0·10–0·15 volumes of a 1% (by volume) solution of acetic acid in redistilled water. The flocculate of fibrinogen is centrifuged off, and can be redissolved in the appropriate volume of untreated plasma to make concentrated fibrinogen solutions of any strength up to ten times normal.

The method proved very effective for joining the cut ends of the sciatic nerve in the rabbit and the dog. Nerve fibres grew slightly faster across such a junction than across the scar of a stitched nerve, and good funicular apposition was secured.

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FIBRIN SUTURE OF HUMAN NERVES

by H. J. Seddon & P. B. Medawar, *Lancet*, **2**, 87–88, 25/7/42

The authors report the use of the concentrated fibrinogen solution introduced by Young & Medawar (1940) in a number of nerve sutures at the Wingfield-Morris Orthopædic Hospital at Oxford. They conclude that the method is of value for the primary suture of divided nerves, but is less useful for secondary suture because of the tension which follows resection of a length of nerve. The material is especially useful for the placing of nerve grafts.

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119

EXPERIMENTAL STUDY OF NERVE SUTURE WITH VARIOUS MATERIALS

by L. Guttmann, *British Journal of Surgery*, **30**, 370–375, April 1943

In spite of wide experience during the last War, and the clear-cut experimental results of Sargent & Greenfield (1919), there is as yet no unanimity of opinion as to the most satisfactory suture material for nerves. The present author, working in the Department of Zoology and Comparative Anatomy at Oxford, made a number of nerve sutures in rabbits, using plain sterile catgut, plain white silk, green silk, waxed and unwaxed black silk, and woman's hair as suture materials. Whatever material was used it always produced undesirable cellular and fibrous reactions, which provided obstacles to the outgrowth of new axons. Woman's hair and plain white silk provoked the least reaction, and of these two, woman's hair, by virtue of its small calibre and smooth surface, allowed the neatest stitching and caused least damage to the nerve.

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120

EXPERIENCES IN THE TREATMENT OF PERIPHERAL NERVE INJURIES WITH AMNIOPLASTIN

by L. Rogers, *British Medical Journal*, **1**, 587, 19/4/41

The amnioplastin used was prepared in the Surgical Unit at Cardiff from placentas obtained from the Obstetrical Department. The method of preparation was that described by Chao, Humphreys & Penfield (1940), and Penfield (1940), and the membranes were preserved in 70% alcohol in stoppered bottles. Before use, the amnioplastin was boiled for half an hour in distilled water.

The membrane was used in 12 cases of injury involving peripheral nerves: ulnar 2, median 4, musculo-spiral 1, great sciatic 2, external popliteal 3. The author refers also to the use of amnioplastin in 8 intracranial cases.

Except in one intracranial case, all wounds healed by first intention. Early functional restoration was noted in most, and freedom from pain in all. The relief of pain, cessation of sweating, and early restoration of normal skin appearances in two cases of causalgia were particularly striking.

The author concludes that amnioplastin is a valuable material for the isolation of nerve elements.

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121

THE REPAIR OF LARGE GAPS IN THE PERIPHERAL NERVES

by F. K. Sanders, *Brain*, 65, 281–337, September 1942

Resection of the damaged portion of nerve is a standard procedure in the repair of the peripheral nerve injuries of warfare, and as a result a considerable gap is often left between the stumps. Direct coaptation, with the limb in the normal position, is thus rarely possible. Methods have been devised for closing these gaps, and they may be classified as follows: *Bridge operations*, in which some sort of bridge is used to carry the new fibres across the gap between the stumps,

namely, nerve grafts, double lateral implantation, nerve flap operations, *suture à distance*, and tubulisation; *manipulative nerve operations*, in which every means is employed to achieve end-to-end apposition of the resected stumps by mobilisation, transposition, flexion of joints followed by nerve stretching, and bulb suture; *nerve crossing*, in which a neighbouring nerve is cut to provide a central stump to which the peripheral stump of the injured nerve may be directly sutured.

The present paper, from the Department of Zoology and Comparative Anatomy, Oxford, is an extensive review of the clinical and experimental literature of these procedures. The author concludes that manipulative operations have been, and are likely to remain, the most widely used methods for the repair of gaps in the peripheral nerves. There is no evidence that such methods as mobilisation and transposition have an adverse effect upon the ultimate quality of recovery. Severe degrees of nerve stretching, however, may cause damage, but the amount of stretch that may be applied to a regenerating nerve without causing damage is not known. There are indications that a stretch of about 10% of the mobilised length of the nerve may be applied without damage, but that a total stretch of as much as 30%, such as may be applied during two-stage operations, may be harmful. In gaps so extensive as to require this amount of stretch to close them, some sort of bridging is probably a preferable procedure.

In addition there are certain well-defined situations where manipulative procedures are relatively ineffective, and here bridge operations are indicated. These situations are:

(*a*) In the repair of the digital nerves (*see* Bunnell & Boyes, 1939).

(*b*) In lesions of the brachial plexus, particularly injuries to C5 and C6, where extensive mobilisation is difficult. Moreover, the difficulty of end-to-end suture in partial lesions of the cords of the plexus makes an inlay graft worthy of trial in this situation, particularly owing to the ease with which such a graft can be fixed in position with the plasma "glue" introduced by Young & Medawar (1940).

(*c*) In lesions of the peroneal nerve, particularly in repairing the very extensive gaps left after resection in traction lesions.

(*d*) In the repair of the facial nerve in the temporal canal (Ballance & Duel, 1932).

Among bridge operations the most successful are nerve grafts. Nerve flaps, *suture à distance*, and tubulisation should be discarded on the experimental evidence. Double lateral implantation is insufficiently documented to warrant any conclusion as to its value on the present evidence, and its performance is attended by considerable risk to the host nerve.

On the available evidence, autografts are the most successful type of graft. They survive, undergo Wallerian degeneration, and can conduct new fibres to the peripheral stump. Although fibres grow slightly more slowly through an autograft than through a normal peripheral stump, the difference (between 3·5 and 2 mm./day in the rabbit) is not sufficient to cause any great delay in the recovery of autografts as compared with end-to-end sutures. The rate of outgrowth is not increased by the use of pre-degenerated, as opposed to fresh, nerve as a graft. Moreover, grafts with preserved vascularisation, consisting of a pedicle taken from a neighbouring nerve, are very rapidly innervated, but the method is not to be recommended for surgical use, on account of damage to the neighbouring nerve. Fresh free autografts are the best except in certain situations (temporal canal) where predegeneration gives a graft of firmer consistency which is more easy to handle.

To allow outgrowth of all its fibres, a graft must exceed, or at least equal, the diameter of its host nerve. Thus in autografts of the thick nerves of man, cable grafts become a necessity. These grafts have never been compared experimentally with full-thickness grafts, but it is significant that the clinical cases showing recovery in autografts are those where either cable grafts, or thin grafts in thin nerves, have been used. There is evidence that necrotic zones occur in thick autografts. Thus, besides being a surgical necessity, cable grafts may possess an advantage in enabling rapid vascularisation of the whole graft to take place. The chief difficulty of these grafts is their preparation and insertion, and it is probable that many of the alleged failures of autografts in the literature have been due to faulty technique. In this instance, both the method of Elsberg (1919), and the plasma "glue" mentioned above, may be of considerable use.

Compared with the results of end-to-end suture, the introduction of an extra point of junction, where ravelling of fibres can occur, must be a point militating against the success of autografts. Too much emphasis must not be placed upon this point until it is known how far the superfluity of fibres produced during regeneration compensates for loss of fibres by deviation. However, some authors (Davis & Cleveland, 1934) have postulated a connective tissue invasion of the lower junction of long grafts, while fibres are still in the upper part of the graft, which causes considerable loss of fibres by deviation upon their arrival at the lower junction. This has been made the basis for a practice of resection and resuture of the lower junction in long grafts after the arrival of fibres, and it is claimed that this gives a juncton with fewer deviated and whorled fibres, and thus a better recovery. However, it has been shown (Sanders & Young, 1942) that the lower junction, even in long grafts, is made by the Schwann cells before the arrival of fibres, and there is no reason to suppose that connective tissue invasion interferes seriously with these pathways. Resuture of the lower junctions of autografts does not appear theoretically to be necessary.

Compared with autografts, the value of homografts is less certain. Experimentally they have been shown to unite with the host nerve, degenerate, become re-innervated, and to be followed by a recovery only a little inferior to that obtained with autografts. Clinically their record is not sufficiently complete to warrant any definite conclusions. Alcohol-fixed grafts, and all other forms of dead nerve grafts, are definitely contra-indicated by both the experimental and the clinical evidence.

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122

THE DEGENERATION AND RE-INNERVATION OF GRAFTED NERVES

by F. K. Sanders & J. Z. Young, *Journal of Anatomy*, **76**, 143–165, January 1942

In the experiments described in this paper from the Department of Zoology and Comparative Anatomy, Oxford, the efficiency of different types of nerve graft was compared by finding the distance which pain fibres had grown through the grafts after short periods (mostly 15 and 25 days) and by careful examination of the histological conditions at these times.

Autografts behave very like normal peripheral stumps. The Schwann cells of the graft survive and multiply, and the myelin breaks up and is removed by macrophages. After a delay of about 9 days at the upper junction, new fibres grow through the graft at 2·0 mm./day, and by 25 days are already medullating in it. At the lower junction there is a maximum delay of 1·7 days, the junction being made by Schwann cells independently of the presence of nerve fibres. This is so even for grafts 5 cm. long, and there is no reason to resort to resuturing a lower junction, apart from a slight tendency of grafts to shorten, which may result in bad junctions in some cases. Predegeneration of the graft does not cause it to be more rapidly penetrated by new fibres.

Homografts set up a considerable lymphocytic reaction, which may lead to partial necrosis. However, proliferation of Schwann cells and myelin break-up occurs, although the latter may be abnormal. Fibres are also able to medullate in the graft, although the rate at which homografts are penetrated by new fibres is slower and more variable than in autografts.

In *homografts stored for 7–21 days in Ringer's solution* at 2° C. the lymphocyte reaction is reduced or absent, although there is a great invasion by macrophages. Schwann cells, nevertheless, survive and proliferate, and new fibres are able

to grow into the graft. They are, however, abnormally thick and rather few in number, and the rate at which they penetrate the graft is variable, although sometimes faster than in control fresh homografts.

Heterografts of dog or rat nerve in the rabbit set up a vast cellular reaction at their edges, and do not degenerate. There is no Schwann proliferation or myelin break-up, and few new fibres enter the graft. A graft of rabbit nerve in a dog produced a very great reaction, by which most of the graft was removed.

Alcohol-fixed homografts are removed by macrophages. New fibres do not enter such a graft, although they may grow well into the bed of macrophages and fibroblasts which replaces it, and so reach the peripheral stump.

A piece of *alcohol-preserved formol-fixed spinal cord* used as a heterograft was encapsulated and attacked by giant cells. New outgrowths proceeded around but not within it.

The authors conclude that in the rabbit the behaviour of autografts provides a good basis for functional recovery. Homografts can also do so, but in some cases set up reactions, which can be reduced by previous storage of the graft. Heterografts, and grafts of dead tissue, provide for reunion of the stumps only after destruction and replacement of the graft, and are thus unlikely to be followed by a successful recovery in man.

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THE HISTOLOGICAL CONDITION OF A NERVE AUTOGRAFT IN MAN

by H. J. Seddon, J. Z. Young, & W. Holmes, *British Journal of Surgery*, 29, 378–384, April 1942

The purpose of this paper is to demonstrate that an autogenous nerve graft in man can function as a living bridge in peripheral nerve reconstructions. Although a certain number of successes have been recorded, the general view held by most British observers is pessimistic and it remained to be proved that the tissue bridging the gap was not merely converted into a fibrous band but remained as viable nerve elements.

The case reported here is of a man of 26, whose median nerve had been divided 10 cm. above the elbow by a bomb splinter. Three months later he was operated on, and the nerve was freed from a large amount of scar tissue. The affected portion of nerve was resected, but the ends could not be brought together without tension, and an autogenous graft of the medial cutaneous nerve of the forearm was therefore inserted and secured by a fibrin coagulum, as described by Young & Medawar (1940). Histological examination of the resected nerve tissue showed that, at the proximal end, normal nerve tissue had not been reached, and although there were some clear bundles, many others were irregularly scattered, the fibres were small and surrounded by proliferating Schwann cells and macrophages, and there was much interfascicular fibrosis. The peripheral end of the resected portion showed only a few scattered bundles and consequently neither side of the gap could be regarded as a suitable bed for the nerve graft.

No sign of recovery was detectable after six months, and in view of the unfavourable histological report on the first specimen, another operation was performed in which the graft, together with a further portion of the central and peripheral stumps of the nerve, was resected. By very extensive mobilisation and extreme flexion of the elbow, the gap was closed without tension.

Histological examination showed that the central nerve bundles had made a good junction with the graft bundles. The latter were well preserved and surrounded by fibrous tissue in which were embedded many small new bundles. The original bundles of the graft contained abundant elongated Schwann cells and had lost their myelin sheaths, but the newly formed fibres, although smaller than the old ones, showed medullation.

Only a few bundles of the peripheral stump made contact with the graft at the original operation and consequently most of the graft bundles were separated from the peripheral stump by scar tissue. The fibres that had grown through the grafts sprouted out in all directions into the junction scar. Some, however, in spite of the unfavourable circumstances, had reached the peripheral stump and were there seen as medullated nerve fibres.

The authors conclude that under suitable conditions transplanted nerves can remain alive and become directly incorporated. The conditions in this case were on the whole unfavourable, but viable graft tissue with newly formed fibres was present six months later. Better results might be expected if the local conditions were good, and if particular attention were paid to the size of the graft to ensure that its cross-section area was approximately equal to that of the nerve stumps.

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[1] [*See BMB* **117**]

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FUNCTIONAL RECOVERY FOLLOWING NERVE GRAFTS AND OTHER TYPES OF NERVE BRIDGE

by E. Gutmann & F. K. Sanders, *Brain*, 65, 373–409, December 1942

In this paper from the Department of Zoology and Comparative Anatomy, Oxford, the authors have made an experimental study of the degree of functional recovery following nerve grafts and other types of nerve bridge. The peroneal nerve of the rabbit was cut in the thigh and repaired by (*a*) unaided union of stumps; (*b*) end-to-end suture; (*c*) various types of nerve graft. The time of onset of motor recovery and its degree in the muscles of the small peroneus group were determined by measuring the return of reflex spreading of the toes in the way described by Gutmann (1942). Recovery of pain sensibility in the skin of the dorsum of the foot was also studied, and the histological conditions of the various grafts as late as 200 days after operation. In this way it was possible to compare the recovery produced after the various procedures more thoroughly than has previously been possible.

Eight out of eight cases of end-to-end suture recovered toe-spreading 56–85 days after operation; 8 out of 10 autografts in 51–98 days; 6 out of 7 fresh homografts in 70–125 days; 8 out of 8 homografts stored for 7, 14 or 21 days in Ringer's solution at 2° C. before insertion in 61–117 days; 2 out of 4 dead alcohol-fixed grafts in 124 and 142 days; and 2 out of 14 unaided unions in 117 and 162 days.

After no procedure was the normal amplitude of movement restored. After recovery, end-to-end sutures and autografts resulted in the amplitude of spreading which came nearest to normality. With fresh homografts and stored homografts there was a recovery-spreading of somewhat smaller amplitude. Spreading of the least amplitude was shown by alcohol-fixed grafts and unaided unions.

Sensory recovery on the dorsum of the foot occurred with end-to-end sutures in 124 and 159 days; with an autograft at 174 days; with fresh homografts in 172–200 days; with stored homografts in 174–200 days; recovery failed to appear before 200 days with all alcohol-fixed grafts and unaided unions.

The structure of the various grafts at 200 days showed the effect of the tissue reactions which sometimes accompany the earlier stages (*see* Sanders & Young, 1942). Autografts were indistinguishable from normal peripheral stumps. Fresh homografts showed fibrotic zones and often spaces with macrophages; the extensive lymphocytic infiltration, often found in the early stages, had disappeared by 200 days. Stored homografts showed some fibrosis, but otherwise resembled normal nerve, there being no trace of the excessive macrophage invasions present in the early stages. Alcohol-fixed nerves showed evidence of destruction and replacement by the host tissues, and consisted of connective tissue masses traversed by new fibres in irregular bundles. They resembled the strand connecting the stumps in unaided unions. Nevertheless at 200 days, grafts, peripheral stumps, and the strand of tissue connecting the stumps in unaided unions all contained myelinated nerve fibres. These were more numerous in normal peripheral stumps, autografts, and Ringer-stored homografts than in fresh homografts, alcohol-fixed grafts, or unaided unions. Fibres also attained a greater diameter in autografts than in homografts, where the largest fibres were restricted to the edges of the graft. The smallest fibre-size was attained in alcohol-fixed grafts. In the two autografts and one homograft in which recovery

failed, the grafts were reduced in diameter, contained many macrophages, and only a few thin nerve fibres.

This study of functional recovery following nerve grafts shows that autografts can survive, become re-innervated, and be followed by as rapid and complete a recovery as after end-to-end suture. Homografts can also be followed by recovery, but this occurs a little later than in autografts and is not so complete—presumably owing to adverse tissue reactions. Previous storage of the graft, which reduces these reactions, promotes a more complete recovery, but does not make it occur significantly earlier. Alcohol-fixed grafts are replaced by the tissues of the host, and are followed by very late and poor recoveries, comparable to those obtained after the unaided union of stumps.

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THE CHEMICAL INHIBITION OF FIBRE REGENERATION AND NEUROMA FORMATION IN PERIPHERAL NERVES

by L. Guttmann & P. B. Medawar, *Journal of Neurology and Psychiatry*, **5**, 130–141, July & October 1942

Acute pain in amputation stumps and peripheral nerve injuries is frequently associated with neuroma formation by the central stumps of the severed nerves. Pain is often relieved by excising the neuroma and taking certain methods to prevent its recurrence. In the past methods have been used which fall roughly into two classes: (i) *surgical and mechanical methods*, involving diversion of the affected stump into muscle or bone, or crushing, ligature, or closure of the end of the stump; (ii) *physical or chemical methods*, in which a length of nerve is destroyed by freezing or cauterisation, or by the injection of substances designed to prevent regeneration.

The authors of the present paper strongly criticise surgical and mechanical methods, on the ground that, while they may prevent escape of nerve fibres from the cut stump, they do not prevent the neuroma formation which is thought to be the cause of pain. A similar criticism of the more radical of these procedures was made by Huber & Lewis (1920).

With regard to chemical methods, the authors report a series of experiments, made in the Department of Zoology and Comparative Anatomy at Oxford, in which they have investigated the effect on neuroma formation of the injection of a number of substances into the tibial nerve of the rabbit. The substances used fall roughly into two classes: (*a*) *fixatives*, i.e. chemical coagulants of protoplasm; and (*b*) various *non-fixatives* which have a specific action, such as the inhibition of amœboid movement or the stimulation of fibroblast proliferation.

The results of these experiments showed conclusively that fixatives as a class were superior inhibitors of neuroma formation to the other substances. Formaldehyde, at concentrations of 20% and over, prevented the formation of either bulbs or adhesions for at least a year after injection. Aqueous gentian violet (1%) was equally effective. Alcohol was effective only for periods of less than 2 months, while other fixatives, such as chromic acid and mercuric chloride, occupied an intermediate position.

Histological investigations showed that the action of the successful inhibitors was a sort of "chemical defence in depth." The effect was due to the maintenance in the injected portion of nerve of an environment which is permeable, but only just permeable, to regenerating nerve fibres. The presence of many nerve fibres was shown to be necessary to the formation of a neuroma. Thus the fixed nerve was only very slowly penetrated by them, and the formation of a neuroma was indefinitely delayed.

The paper concludes with a discussion of the application of the technique to the injection of human nerves.

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126

LOCAL APPLICATION OF SULPHANILAMIDE TO PERIPHERAL NERVES

by W. Holmes & P. B. Medawar, *Lancet*, **2**, 334–335, 19/9/42

In this paper from the Department of Zoology and Comparative Anatomy, Oxford, the authors report a study of the effect of sulphanilamide applied around the sciatic nerve of the rabbit. The nerve can withstand as much as 1 g. of the drug packed into the thigh, but with 2 g. there is interruption of the nerve fibres and complete Wallerian degeneration. The test is of course a severe one. The operation site is clean and bloodless. However, they conclude that, since sulphanilamide is sufficiently soluble to exert a damaging effect on nerve, it should be used with caution at operations in which peripheral nerve trunks are exposed.

TRACTION INJURIES OF NERVES

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TRACTION INJURIES TO THE LATERAL POPLITEAL NERVE AND TRACTION INJURIES TO PERIPHERAL NERVES AFTER SUTURE

by W. B. Highet & W. Holmes, *British Journal of Surgery*, **30**, 212–233, January 1943

In this paper from the Nuffield Department of Orthopædic Surgery and the Department of Zoology and Comparative Anatomy, Oxford, the authors have made a study of traction injuries and the similar conditions which are produced by attempts to stretch nerves too strongly after resection and suture. Eight cases of traction injury to the lateral popliteal nerve were treated surgically, and the lesions were examined histologically.

They found that the traction lesion is characterised by much more extensive damage to the nerve-trunk than is found after injury by incision, laceration, or gunshot wound. The pathological changes in the nerve extend far above the site of obvious damage, in the form of fibre degeneration, intraneural fibrosis, and vascular abnormality. The connective tissue sheaths of the nerve undergo rupture to a varying degree; thus the nerve may be completely divided, or bear a fusiform neuroma, or show macroscopical continuity. Spontaneous recovery did not take place even in cases in which nervous tissue was continuous throughout the lesion. Regenerating nerve-fibres succeeded in crossing the lesion, but they remained small in diameter and most of them failed to become myelinated. In three cases end-to-end suture was performed after an extensive resection of the lesion: closure of the gap was obtained by extensive mobilisation of the nerve and flexion of the knee. No recovery took place in these cases. In one case in which a less extensive resection was necessary a good recovery is in progress. A further exploration of the nerves which failed to show recovery after suture was carried out. Histological examination showed pathological changes similar to those following the original lesion, but even more severe and extensive.

The authors conclude that failure of recovery after extensive resection and suture may be due to injury inflicted on the nerve during post-operative extension of the joint.

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THE EFFECTS OF STRETCHING NERVES AFTER SUTURE

by W. B. Highet & F. K. Sanders, *British Journal of Surgery*, **30**, 355–369, April 1943

This paper from the Nuffield Department of Orthopædic Surgery, and the Department of Zoology and Comparative Anatomy, Oxford, reports a series of experiments on nerve stretching made as a corollary to the clinical work of Highet & Holmes (1943).

Gaps in the external popliteal nerves of dogs, following extensive resection of the nerve in the thigh, were closed by flexion of the knee and suture of the stumps with the limb in this position. After keeping the knee flexed for 14 days in a plaster cast, the nerve was stretched by extending the knee either (*a*) rapidly, by the animal's own movements, or (*b*) gradually, with a "turnbuckle" plaster [a pair of casts enclosing a limb above and below a joint and connected by a screw. By turning the screw, the casts are pushed apart and

the joint is forcibly extended]. The site and extent of nerve stretching was determined by the changes in position of a line of silver clips placed along the nerve at operation, and photographed by X-ray before and after stretching.

In the normal animal some elongation of the nerve over its whole length from the sciatic plexus to its entry into the shank musculature accompanies extension of the knee, but by far the greatest part of the increase in the length of the course of the nerve during knee extension in the normal animal occurs by straightening out of the tortuosity of the nerve.

When gaps have been closed by flexion of the knee the extra distance is made up by elongation of the nerve. Straightening out of tortuosity plays only a minor part. The elongation thus produced is not distributed uniformly along the length of nerve. Scar tissue formed about the suture line binds the nerve to its bed, and disproportionate stretching of the peripheral stump occurs. After such stretching the nerve returns to its original length with each subsequent flexion of the knee. Permanent elongation of the nerve does not take place in the first 35 days after operation.

The above procedure produced histological damage of the following kinds: (i) extensive, abnormal, degeneration in the central stump, (ii) where the suture line is not bound by scar tissue, separation of the stumps can take place, (iii) rupture of Schwann tubes where stretching is at all severe, (iv) extensive œdema and fibrosis both without and within nerve bundles, causing considerable disruption of the pattern of the nerve. All these factors tend to reduce the chances of a recovery of a good quality.

Rapid nerve stretching did not cause any more damage than slow stretching, except, perhaps, in so far as separation at the suture line occurred more frequently.

From the results of these experiments the authors conclude that there is probably an upper limit to the size of gap that can be overcome by post-operative nerve stretching in man, and be compatible with recovery.

REFERENCE

[1] Highet, W. B., & Holmes, W. (1943), *Brit. J. Surg.*, 30, 212

[1] [*See BMB* 127]

FACTORS AFFECTING RECOVERY AFTER NERVE INJURY

[*In spite of the great amount of material available from the study of nerve injuries in man, there is still very little thoroughly reliable information as to the factors which influence the degree of recovery. Cases have generally followed war wounds or accidents: the nerve has been injured over varying lengths; the blood supply has been damaged, or there has been sepsis; surgical treatment has varied from case to case, and these and many other variables have combined to make comparison of clinical cases difficult.*

In the two papers summarised below, Drs. E. Gutmann and L. Guttmann, working in the Department of Zoology and Comparative Anatomy at Oxford, have attempted to define more closely the various factors which influence motor and sensory recovery after nerve injuries. They have done this by means of animal experiments in which all those variables which are the disadvantage of clinical material can be separately and accurately controlled.]

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FACTORS AFFECTING RECOVERY OF MOTOR FUNCTION AFTER NERVE LESIONS

by E. Gutmann, *Journal of Neurology and Psychiatry*, 5, 81–91, July & October 1942

In this paper the author has attempted to define the influence on motor recovery of (i) the nature of the lesion, (ii) its level, (iii) interference with blood supply of the limb, (iv) age of the subject, (v) infection, and (vi) delay of suture.

The animals used were rabbits and the peroneal nerve was interrupted at an initial operation in one of four ways: (1) by crushing at a single point with fine forceps; (2) by severance followed by suture with either cockerel plasma or fine white silk stitches; (3) by crushing with broad forceps over a length of 4 cm.

Motor recovery was followed by almost daily examination of the toe-spreading reflex of the hind limb, a function performed by muscles innervated by the peroneal nerve. Other criteria of muscle recovery were also examined, namely: (*a*) the response to electrical stimulation of the nerve, (*b*) the direct excitability of the muscle, (*c*) the circumference of the limb in the region of the denervated muscles, (*d*) the weight of the muscles, (*e*) the disappearance of fibrillation.

After crushing the peroneal nerve at the knee, nerve fibres first return to the muscle after about 10 days, contraction on stimulation of the nerve after 18–20 days, first reflex spreading of the toes after about 25 days. Full amplitude of spreading is not achieved until 33 days, and for a time spreading may exceed the normal amplitude, although it eventually regains normality. The circumference of the limb with denervated muscles begins to increase, and the threshold of these muscles to direct stimulation to decrease, before reflex spreading, and sometimes before even electrical excitability via the nerve appears. Fibrillations continue in the muscle about 2 weeks after the first appearance of reflex function, but the normal weight of the muscles is not regained until at least 12 weeks after the first reflex spreading.

It was also found after crushing the nerve that when the lesion is more distant there is a longer delay between arrival of fibres at the muscle and the first occurrence of contraction on stimulating the nerve. Moreover the time between the appearance of reflex function and its completion is greater after more distant than after near lesions. The rate of advance of regeneration, however, is not slower with more distant lesions. It has a value of $2{\cdot}77 \pm 0{\cdot}09$ mm./day after a latent period at the lesion of 18·2 days.

The author found that after severance and suture all the processes of recovery are slower than after crushing the nerve. The rate of advance of regeneration is $1{\cdot}69 \pm 0{\cdot}34$ mm./day with a latent period of 27·7 days. The delay between arrival of fibres and the return of reflex function is greater than after crushing. After the first reappearance of reflex spreading there is only a gradual increase in amplitude, and a normal amplitude is never attained.

Recovery after crushing the nerve over a length of 4 cm. is later and less complete than after a local crush. Ligature of the popliteal artery and vein does not delay recovery, and infection does not delay recovery unless it affects the nerve itself. Age, however, markedly affects the rate of recovery, which occurs much earlier in young animals.

Cross-unions of the tibial and peroneal nerves are also followed by a recovery of toe-spreading, and this type of union has been used to study the effect of delay of suture on recovery. Delay of suture reduces the degree of recovery and retards its onset, but the effect is not marked unless the delay exceeds 6 months.

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FACTORS AFFECTING RECOVERY OF SENSORY FUNCTION AFTER NERVE LESIONS

by E. Gutmann & L. Guttmann, *Journal of Neurology and Psychiatry*, 5, 117–129, July & October 1942

The experiments described in this paper were undertaken at the same time as those on motor recovery summarised above, and had three main objects: first, to delimit the maximal and autonomous areas of the skin served by various nerves in the hind limb of the rabbit; secondly, to show the manner in which shrinkage of the insensitive area left after denervation takes place, and the parts played in this shrinkage by (*a*) recovery in the zone of overlap between the interrupted and its adjacent nerves, (*b*) recovery in the autonomous zone of the interrupted nerve; and thirdly, to show how recovery is affected by such factors as the nature of the lesion, its distance from the skin, age of the animal, and infection.

The skin areas innervated by the peroneal, tibial, sural, saphenous, and postero-lateral cutaneous nerves are described. In these cases the maximal zone was determined by the area of remaining sensibility after section of all the adjacent nerves, leaving the nerve in question intact. The autonomous zone was determined by the area of analgesia left some time after isolated section of the nerve in question, the prevention of regeneration from the central stump by extensive resection, and by waiting for the process of recovery in overlap zones to run its course.

From a study of the extent of the analgesic zones found at various times after these two types of operation the authors conclude that recovery of analgesic area is a complex process comprising three main phases: (i) recovery in zones of overlap by the progressive resumption of function by fibres of adjacent nerves; (ii) extension of these fibres into the denervated area [a histological investigation of this phenomenon has been made by Weddell, Guttmann & Gutmann, 1942]; (iii) regeneration of the interrupted nerve.

The first process, recovery in overlap zones, is generally complete 2 to 4 weeks after interruption of the nerve in adult animals, but occurs within a few days of operation in young animals. It is peculiarly susceptible to various factors such as local damage to the skin supplied by adjacent nerves, transient block of these nerves as a result of operation, and all processes such as infection, sores, narcosis, and old age.

The third process, which comprises recovery in the autonomous zone, and is due to regeneration, proceeds in general in a downward direction. In large areas recovery often advances faster at the edges than in the centre, so that the analgesic area shrinks concentrically. This pattern of recovery, i.e. centrifugal advance and concentric shrinkage, was observed in all the nerves examined.

The authors found that the nature of the lesion profoundly affects the time and degree of recovery. After suturing the nerve the recovery was slower, less regular, and definitely of an inferior degree to that obtained after simply crushing the nerve at a single point. Crushing the nerve over a length of 4 cm. was also followed by recovery inferior to that after a single crush.

The rates of advance of regeneration also were different. After crushing, the rate of advance was 3·35 mm./day, with a latent period of 22 days; after suturing the rate was 2·46 mm./day, with a latent period of 40 days. Greater variability after suturing makes this second estimate less reliable.

The rate of advance of the margin of algesia in the autonomous zone of the peroneal nerve after crushing at various levels was found to be $1 \cdot 98 \pm 0 \cdot 09$ mm./day. After suturing it was $1 \cdot 57 \pm 0 \cdot 15$ mm./day. After crushing the rate was higher when the nerve was crushed at the ankle than when it was crushed in the thigh.

REFERENCE

[1] Weddell, G., Guttmann, L., & Gutmann, E. (1941), *J. Neurol. Psychiat.*, **4**, 206

[1] [*See BMB* 136]

THE ACTUAL PROCESSES OF NERVE REPAIR

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NERVE REGENERATION AFTER IMMEDIATE AND DELAYED SUTURE

by W. Holmes & J. Z. Young, *Journal of Anatomy*, **77**, 63–96, October 1942

Studies of the histology of nervous regeneration have previously been restricted to the period following a primary suture (*see* Cajal, 1928), whereas in man suture is often much delayed.

In this paper from the Department of Zoology and Comparative Anatomy, Oxford, the authors have re-investigated the histological aspects of regeneration in nerves, laying special emphasis on the process of re-innervation of stumps which have been allowed to degenerate for a long time. They emphasise that during degeneration the pattern of a nerve is maintained by the endoneurium and neurilemma, a Schwann tube being formed in place of each original fibre. Each tube gradually contracts, finally reaching about half the diameter of the original fibre. Macrophages enter these tubes and remove the remains of axons and myelin. They are abundant from about the 8th to the 25th day and thereafter disappear gradually, some persisting for a year or more. The protoplasm of the Schwann cells increases in amount and after nuclear division elongated cells are found, lying side by side in the larger tubes. In the early stages the Schwann cells do not entirely fill the tubes. They gradually replace the macrophages and when the tube is fully contracted its whole cross-section is filled with fibrillar Schwann protoplasm, the nuclei becoming extremely elongated. Such Schwann cells may easily be mistaken for nerve fibres, especially when stained with silver. In the early stages the Schwann cells probably move within the tubes. Certainly they emerge at the end of the peripheral stump and are the main agent for leading fibres back into the old tubes. Growth and mitotic division take place in the Schwann tissue which has migrated from the peripheral stump. The tip of the outgrowth was found to have reached to an average distance of 1·4 mm. in 15 days, and 2·2 mm. in 25 days. But the outgrowth does not continue progressively if the stump is left un-innervated.

Normal nerve fibres in the walls of the intraneural blood-vessels usually send out collaterals into the nerve tissue of isolated degenerated stumps. They remain very small and are rarely medullated, but are sufficient to produce a reflex response on stimulation and an outgrowth of nerve fibres from the peripheral end if the stump be again cut. The endoneurium and perineurium of a long-degenerated stump become moderately but not excessively collagenised. The diameter of the whole nerve may decrease by as much as one-half.

When new fibres grow into a freshly cut peripheral stump they run along the inner walls of the Schwann tubes. Where possible they grow along the surfaces of Schwann cells, but do not at first lie within them. As many as twenty fibres may enter a single tube. One or more, rarely several, of these increase in diameter, and become surrounded by Schwann cell protoplasm and medullated. The others remain for a while around the periphery of the tube and presumably they ultimately atrophy.

The power of a central stump to send out new fibres is not reduced if it be severed a second time and then sutured, either within a week or after an interval as long as a year. The power of a peripheral stump to put out Schwann cells is greatest if it be cut a second time some 2–3 weeks after its first severance. Thereafter this power declines, and unions made with peripheral stumps degenerated for more than 100 days are often unsatisfactory. However, once within a peripheral stump which has been degenerated for a long time, fibres may proceed as rapidly as into a freshly cut stump. Fewer fibres penetrate into a stump which has been degenerated for a long time than into a freshly cut one. Medullation proceeds much more slowly after delayed suture. There are thus various other factors, in addition to atrophy of the end-organs, which are likely to reduce the effectiveness of recovery where suture is made after a long delay.

The authors conclude that the processes of union of stumps and the regeneration of a new functionally efficient stretch of nerve are less satisfactory after the longer periods of degeneration. Delay in suturing for 1 or 2 months does not prejudice the chances of recovery, and may even improve them; longer delays, especially those greater than 5 or 6 months, produce conditions which at least are liable to retard recovery, and may permanently prevent its completion.

REFERENCES

Ramón y Cajal, S. (1928), *Degeneration and Regeneration of the Nervous System*, Oxford

132

THE OUTWANDERING OF CELLS IN TISSUE CULTURES OF NERVES UNDERGOING WALLERIAN DEGENERATION

by M. Abercrombie & M. L. Johnson, *Journal of Experimental Biology*, **19**, 266–283, December 1942

These authors, working in the Department of Anatomy and Zoology, Birmingham, have investigated the effect of various periods of degeneration on the power of outgrowth of the Schwann cells which are so important for making the union between nerve stumps. They used the technique of tissue culture. Ingebrigtsen (1916) first showed that these cells emerge from a piece of nerve explanted into a culture medium in vitro. This growth takes place only if the piece of nerve which is explanted has been severed some time previously.

The present authors were able to measure the degree of activity at various times after severance. They found that, in the peripheral stump, Schwann cell activity begins on the 2nd day after cutting, and from the 4th day rises rapidly to

a peak at the 19th–25th day. It then falls quickly up to about the 60th day and afterwards more slowly. Activity is still appreciable more than a year after cutting. These changes of activity according to the time of degeneration are shown by thigh, knee and shank regions of the peripheral stump. The knee region, and the shank (which is 8 cm. distal to the initial cut) are more active than the thigh region, especially in the early days of degeneration.

In the central stump, activity is at first confined to a few mm. immediately adjacent to the cut. From the 2nd to the 4th day after cutting, the central stump is more active than the peripheral stump, but thereafter it is much less active. Its maximum activity never reaches more than 10 % of the maximum activity of the peripheral stump. Activity is still appreciable more than a year after the cut was made. The more proximal part of the central stump, at first inactive, begins to show slight Schwann cell activity after 29 days and is still active after more than a year.

Since Schwann cells probably play an important part in forming the junction when severed nerves are repaired, this work indicates the optimum from this point of view for making grafts or sutures. The experiments indicate that the Schwann cells will be more active in joining together two nerve stumps if the nerve or nerve graft is left a few (say 10–20) days to degenerate before making the repair; and that (in the rabbit) the optimum time for suture is passed 25 days after the nerve is cut.

REFERENCE

Ingebrigtsen, R. (1916), *J. exp. Med.*, **23**, 251

133

RECOVERY OF FIBRE NUMBERS AND DIAMETERS IN THE REGENERATION OF PERIPHERAL NERVES

by E. Gutmann & F. K. Sanders, *Journal of Physiology*, **101**, 489–518, March 1943

The process of regeneration of a nerve can be divided into two contiguous phases: (i) that of *outgrowth*, which has as its result the arrival and connexion of fresh axons with the periphery, and (ii) that of *reconstitution*, whereby the numbers, diameters, and medullation of the fibres are restored. This latter phase of regeneration has received little attention until now. The authors of this paper, from the Department of Zoology and Comparative Anatomy, Oxford, have investigated the process of reconstitution by means of counts and measurement of the fibres in the peroneal nerve of the rabbit at intervals after either crushing the nerve, or cutting and repairing it by suture or nerve graft.

The peroneal nerve normally contains 6000–9000 medullated nerve fibres, varying in size from 1 to 20 μ. The frequency distribution of fibre diameters is a bimodal one, with peaks at 2–3 and 13–14 μ. Only after crushing the nerve were the normal number and distribution of the fibres in the peripheral stump eventually restored. Reconstitution was complete at about 300 days after operation. As late as one year after suture, or 200 days after nerve grafting, neither the number nor the pattern of fibres was restored.

It is of interest that the fibres in the central stump above the lesion were found to shrink during the early stages of reconstitution, as though they were being depleted by an outflow.

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THE RATE OF REGENERATION OF NERVE

by E. Gutmann, L. Guttmann, P. B. Medawar, & J. Z. Young, *Journal of Experimental Biology*, **19**, 14–44, May 1942

In this paper from the Department of Zoology and Comparative Anatomy, Oxford, the authors report the results of measuring the rate of advance of regeneration along nerves in the rabbit in five different ways. Not all the methods gave the same result, and the authors conclude that the concept " rate of regeneration " is far from being simple. When the rate of advance of the growing axon tips is studied, a higher rate is recorded than when the times necessary for functional recovery are considered. In the latter case, the experiment measures the rate of advance, not of the tips of the regenerating axons, but of completed nerve fibres, able to function.

The factors determining the time which elapses between suture and recovery are therefore: (i) the " scar delay," which includes the time necessary for the fibres to undergo retrograde degeneration, branching, and the relatively slow process of growth across the suture scar; (ii) the rate of progress down the nerve of a process of " functional completion," which lags behind the more rapidly advancing axon tips.

The " scar delay " is nearly constant after all well-made sutures (7·3 days). After crushing the nerve it is only slightly shorter (5·2 days). There is a further delay before the process of functional completion begins to advance down the nerve, so that there is a total latent period of 36 days after suture and 20 days after crushing.

The rate of advance of the axon tips was determined by finding the furthest point from the lesion at which nociceptive reflexes could be elicited by pinching the nerve. This rate is not significantly different in the three divisions of the sciatic nerve, or after interrupting the nerve at different distances from the nerve-cell bodies. After suture it has a value of 3·5 and after crushing of 4·4 mm./day.

The rate of advance of functional completion of nerve fibres was measured by making lesions at various levels and studying: (*a*) the time necessary for return of response to nociceptive stimuli to a given point on the skin, and (*b*) the time for recovery of a given motor function, namely, spreading of the toes. Both methods gave rates of 2·0 mm./day after suturing, 3·0 mm./day after crushing.

Comparison of the times of recovery of muscles at varying distances from a lesion gives an estimated rate of advance of functional completion of 2·2 mm./day after crushing a nerve, but this method is only approximate in the rabbit.

Analgesic areas on the foot shrink during recovery at a rate of 2·1 mm./day after crushing and 1·6 mm./day after suture.

In rabbits one month old, the rate of advance of the axon tips is not greatly different from that in adults, but the scar delay is less, and functional completion proceeds more rapidly.

It is concluded, from a study of the experimental results and from published data, that the process of functional completion proceeds down the nerve faster than the accepted 1 mm./day both in experimental animals and in man.

[Until recently, knowledge of the histology of nerve degeneration and regeneration was largely based on the changes which occur in nerve trunks, and the cutaneous nerve plexuses had received relatively little attention. The series of papers reviewed below (BMB 135–138) gives an account of recent advances in this field. They are mainly based upon a study of total preparations of large pieces of skin, stained intravitally with methylene blue. The work was done in the Departments of Human Anatomy and of Zoology and Comparative Anatomy, Oxford.]

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THE EARLY STAGES IN THE DEGENERATION OF CUTANEOUS NERVE FIBRES

by G. Weddell & P. Glees, *Journal of Anatomy*, **76**, 65–93, October 1941

Weddell (1941) gave a descriptive account of the normal innervation of the skin of the rabbit's ear, and the present paper continues with a description of the changes which occur in the cutaneous nerve plexuses between 12 and 336 hours after nerve section. The changes follow the pattern generally accepted for nerve trunks, although they differ from them in certain particulars.

After nerve section the axons were found to swell up and disintegrate, the last portions to be affected being in the region of the nodes of Ranvier. Disintegration was most rapid in the non-medullated axons, and proceeded relatively more slowly in medullated fibres, the slowest fibres of all to degenerate being those of the greatest diameter. However, some of the largest fibres showed precocious degeneration, and there were resistant fibres throughout the range of size.

Degeneration of myelin followed its typical course. First of all a reticular network appeared throughout the myelin sheath, followed by a break-up of the myelin into droplets of various sizes, which form the so-called "ellipsoids" or

"digestive chambers." These are gradually resorbed, and by 336 hours after nerve section not one remains in the cutaneous plexus.

Between 96 and 168 hours after nerve section the Schwann cells of the cutaneous nerve plexus proliferate and come to surround the digestive chambers. By 336 hours degeneration is complete, and each nerve fibre is replaced by its connective-tissue sheath containing strands of Schwann protoplasm with elongated nuclei.

The authors could find no evidence of the supposed phagocytosis of myelin remains by Schwann cells.

In normal skin from both rabbit and man a certain number of degenerating fibres were found. These were more common in regions which are constantly subjected to minor traumata, such as the pressure point of the elbow. The authors conclude that the nerve fibres in such regions, like the lymph capillaries, are probably in constant flux, a cycle of degeneration and regeneration constantly taking place and accompanying minor irritative changes.

REFERENCE

Weddell, G. (1941), *J. Anat. Lond.*, **75**, 346

136

LOCAL EXTENSION OF NERVE FIBRES INTO DENERVATED AREAS OF SKIN

by G. Weddell, L. Guttmann, & E. Gutmann, *Journal of Neurology and Psychiatry*, **4**, 206–225, July & October 1941

Pollock (1920) found clinically that the areas of sensory loss after nerve injuries can shrink circumferentially before any regeneration can have taken place from the central stump. The present authors made an experimental investigation of this phenomenon in rabbits.

In a series of animals the sural nerve (supplying a boot-shaped area on the outer aspect of the heel) was divided on one side and resected to avoid re-innervation of the peripheral stump. On the other side the tibial and peroneal nerves were divided, the sural nerve being left intact. The changes in extent of the skin areas left analgesic after these operations were mapped by both pinprick and faradic stimuli, and the skin of the region was removed at intervals from different animals, stained with methylene blue, and mounted as a total preparation.

The area of analgesia was always found to be more extensive immediately after nerve section than at later stages. Sensibility in the recovered zone was restored by two processes: (i) by re-adjustment of the function of fibres in the zone of overlap between the distribution of the cut nerve and neighbouring cutaneous nerves, (ii) by local extension of the areas innervated by nerves adjacent to the cut nerve, due to growth of new fibres through the cutaneous nerve plexuses.

The clinical terms *autonomous*, *maximal*, and *intermediate* zones, applied to the overlapping distribution of cutaneous nerves, have thus a dynamic as opposed to a static anatomical significance, for directly after nerve section, processes begin which alter the extent of these zones.

REFERENCE

Pollock, L. J. (1920), *J. comp. Neurol.*, **32**, 357

137

AXONAL REGENERATION IN THE CUTANEOUS NERVE PLEXUSES

by G. Weddell, *Journal of Anatomy*, **77**, 49–62, October 1942

In this paper the methylene-blue technique was used to analyse the pattern of regeneration of cutaneous nerve fibres, and to correlate the results of sensory tests with the histology of regeneration. Skin was removed from the ears of rabbits at intervals of up to 12 months after the main dorsal ear nerve had been interrupted by crushing or by severance. The area of analgesia to pin-prick and to approximately threshold faradic stimuli was plotted at intervals during regeneration, and finally just before removal of the skin.

After nerve interruption there was an initial small, slow diminution of the area of sensory loss before regeneration of the fibres of the interrupted nerve actually took place. This went on for about 14 days after crushing, or for up to 4 weeks after nerve severance, and was found to be partly the result of the sprouting of fibres from neighbouring normal nerves. This confirmed the conclusion reached in an earlier paper (Weddell, Guttmann, & Gutmann, 1941). With the beginning of true regeneration, the rate of advance of the border of analgesia increased considerably, and proceeded until the whole area of analgesia recovered its sensibility.

Histologically, nerve fibres were found first to cross the scar, each fibre which succeeded in crossing throwing out a number of collaterals, and then to advance along the original main nerve fasciculi beneath the skin. After these had become re-innervated the nerve fibres pursued a tortuous course through the cutaneous nerve plexuses towards the surface of the skin, following the Schwann cell pathways which retained the pattern of the plexuses of the normal ear. The growing fibres lay at first upon the surface of the Schwann cytoplasm. Later, as the fibres matured, they became enclosed within it. As the fibres increased in diameter many of their collaterals underwent degeneration. More persistent collaterals were found after nerve section than after crushing.

The margin of regeneration as indicated histologically was usually found to be about 5 mm. in advance of the border from which the first nociceptive responses could be elicited. The author considers this discrepancy to be due to the following factors: (i) that the finest growing tips of the nerve fibres are not sufficiently mature, and are situated too far below the surface of the skin to initiate and conduct impulses in response to nociceptive stimuli; (ii) that fibres in advance of the margin of algesia, even when mature, are too few in number to give rise to a reaction on the part of the animal.

The author also found that there was a zone at the border of algesia where thresholds were raised (i.e. more random pricks, or a stronger faradic stimulus, were required to elicit a response). In such a zone many hair follicles are supplied by single nerve fibres, and the nerve nets beneath the epithelium are isolated and do not form an interdigitating series as in a normal ear. Regeneration in this zone is not yet complete.

REFERENCE

[1] Weddell, G., Guttmann, L., & Gutmann, E. (1941), *J. Neurol. Psychiat.*, **4**, 206

[1] [*See BMB* 136]

138

OBSERVATIONS ON THE STRUCTURE OF THE CONNECTIVE TISSUE SHEATHS OF CUTANEOUS NERVES

by P. Glees, *Journal of Anatomy*, **77**, 154–159, January 1943

In this paper the author describes the structure of the collagenous enveloping sheaths of the fibres in the cutaneous nerve plexuses. Individual cutaneous bundles are surrounded by a *perineurium* consisting of longitudinal and oblique collagen fibres, the latter forming a double spiral. Each fibre has in addition an *endoneural sheath*, which consists of both longitudinal and oblique spirally arranged collagen fibres on the larger, and of longitudinal collagen fibres only on the smaller nerve fibres. Each nerve fibre is thus enclosed by a collagenous tube running all the way to its end-organ.

Following denervation, the perineurium and the endoneural tubes, which are kept distended by the hypertrophied Schwann cells, preserve the old pattern of innervation. The new nerve fibres grow down into the old endoneural tubes, and are thus forced to repeat the old pattern of ramification.

THE BLOOD VESSELS OF PERIPHERAL NERVES

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THE BLOOD SUPPLY OF NERVES

I. Historical Review.

II. The effects of the exclusion of its regional sources of supply on the sciatic nerve of the rabbit.

by W. E. Adams, *Journal of Anatomy*, **76**, 323–341 & **77**, 243–250, July 1942 & April 1943

It is sometimes stated that little or nothing is known about the anatomical and physiological aspects of the vascularisation of nerves. The present paper, from the Anatomy

Department, Leeds University, shows that this view is erroneous. The author has collected, from scattered and often relatively inaccessible references, a great deal of information on the distribution of the *vasa nervorum*, and the physiological effects of interference with blood supply, producing a summary which is especially valuable.

Generally speaking the blood supply of a nerve is derived from regional vessels which also contribute to a longitudinal pathway along the nerve. The ganglia associated with the nerves receive a similar, but even richer, blood supply.

Experimental evidence indicates that cessation of blood-supply to any part of a nerve induces a complete nerve block. The large rapidly conducting fibres are the first to be affected, but the changes are reversible, and restoration of the circulation restores the capacity of the nerves to conduct, initiating at first exaggerated responses—the familiar "pins and needles." There is no evidence that other subjective phenomena, such as pain and vertigo, can result from ischæmia.

The second paper contains the results of an attempt to produce degeneration of the sciatic nerve of the rabbit experimentally by ligation of one or more of its regional sources of vascular supply. Ligation of the inferior gluteal artery alone produced no degeneration or other obvious histological change in the nerve in 8 experiments. In a further 12 experiments the effect of ligating all the vessels in the thigh which supply the sciatic nerve was investigated. In 10 cases either no degeneration, or degeneration of an insignificant degree, took place. In the remaining 2 cases extensive degeneration occurred, but it was not certain whether this could be attributed to manipulation of the nerve, or to some variation in the intrinsic vascular pattern in these cases.

The author concludes that severe disturbance is unlikely to follow such surgical procedures as the mobilisation of nerves, where long stretches of nerve are freed from surrounding tissue, and thus are cut off from their regional sources of vascular supply.

REGENERATION IN THE CENTRAL NERVOUS SYSTEM

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THE PROBLEM OF NEURONAL REGENERATION IN THE CENTRAL NERVOUS SYSTEM

I. The influence of spinal ganglia and nerve fragments grafted into the brain.

II. The insertion of peripheral nerve stumps into the brain.

by W. E. Le Gros Clark, *Journal of Anatomy*, 77, 20–48 & 251–259, October 1942 & April 1943

While the great regenerative power of peripheral nerve axons has become a commonplace of neurology, there is still some doubt whether the axons of the central nervous system possess a similar power. The experiments described in these two papers from the Department of Human Anatomy, Oxford, were undertaken in order to determine the limits of the regenerative processes which may occur in the brain. Those described in the first paper were in essence a repetition of the experiments of Tello (1911), which appeared to demonstrate not only that neurones of the central nervous system have a capacity for regeneration similar to those of peripheral nerves, but that this capacity is stimulated to expression by neurotropic substances elaborated in degenerating nerves.

Pieces of the peripheral stump of sciatic nerves degenerated for 10–14 days were placed in the brain of another animal immediately dorsal to the corpus callosum, extending transversely between the hemispheres. In some experiments spinal ganglia were grafted into the brain alongside the nerve fragments. Only 3 out of 13 pieces of grafted nerve were found to contain a very few nerve fibres 13 to 20 days after implantation. In two of the cases the nerve fibres were traced to fasciculi accompanying newly formed blood vessels. In no case could the fibres be traced to the host brain, although the Schwann tissue of the graft was in continuity with the tissues of the host brain, and there was no fibrous barrier. In some experiments, however, the fibres in the white matter were found disposed in fasciculi oriented towards the graft, exactly as Tello observed. This appearance was found to result from a traction effect exerted on the host tissue by the grafted tissue and the cellular reaction which accompanies its implantation.

The cells of grafted spinal ganglia showed great regenerative activity, and fibres grew from them into the zone of infiltration separating the graft and the host brain.

All the grafts of the above series of experiments were homografts, and it is possible that the cellular reaction to the foreign tissue adversely affected the result. In the second series the peripheral stump of the facial nerve was inserted directly into the brain, which combined the advantages of an autograft with retention of the vascular supply of the graft. Proliferated Schwann tissue grew out into the tissues of the brain, and was occasionally accompanied by nerve fibres which grew down the implanted nerve from the cut central stump outside the skull. A few regenerating fibres were also found whose origin was the blood vessels. No evidence was found of regeneration of the cerebral neurons, although these came into the closest contact with Schwann cells and regenerating peripheral fibres.

The author concludes that the intrinsic fibres of the brain have little or no regenerative capacity.

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OBSERVATIONS ON DENERVATED MUSCLE

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EFFECT OF ELECTROTHERAPY ON DENERVATED MUSCLES IN RABBITS

by E. Gutmann & L. Guttmann, *Lancet*, 1, 169–170, 7/2/42

The authors recall that it is just over 100 years ago that John Reid (1841) published in Edinburgh a paper on the relations between muscular contractility and the nervous system, in which he described for the first time the beneficial effect of a galvanic current on denervated muscles. Since then, opinions on the value of electrotherapy in the treatment of peripheral nerve lesions have varied greatly, and available experimental results do not appear to be conclusive.

The present paper reports a study carried out in the Department of Zoology and Comparative Anatomy, and the Nuffield Department of Surgery at Oxford, on the effect of the galvanic current on denervated muscles in the rabbit, with particular attention to: atrophy of the denervated muscles; electrical excitability and contractility; time and quality of recovery of function. The muscles used were those in the group supplied by the peroneal nerve, which was crushed in both limbs by fine forceps approximately 80 mm. from its entry into the *peroneus longus* muscle.

In all cases systematic exercise by galvanic current was carried out daily on one limb for 15–20 minutes, at a current strength of 4–6 milliamperes by means of a dry battery apparatus of 120 volts. The other limb was left untreated as a control. During the first 2 weeks after operation, electrotherapy did not prevent atrophy, but in the subsequent weeks the decrease in the circumference on the treated side was slower in all animals and in no case was the ultimate atrophy so great as on the untreated side. In all cases the exercise accelerated the recovery from atrophy, after the muscles had become re-innervated, the treated side attaining its normal measurement more quickly than the untreated side.

During the treatment individual denervated muscles were subjected to faradic stimulation via the skin and it was found that although both the galvanically exercised and the control denervated muscles showed a progressive decrease in excitability, this was less marked on the treated side.

At various intervals after recovery sections were removed for biopsy, and in all cases there was a striking difference in the appearance of the exposed muscles. Those on the treated side were larger and more normal to the naked eye. Sections showed the treated muscles to have larger fibres, more definite striation, and less fibrosis than those on the untreated side. Muscles situated superficially showed the more pronounced benefit from the treatment.

The results of these experiments leave no doubt in the minds of the authors that electrotherapy in the treatment of peripheral nerve lesions has a sound scientific basis.

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THE CLINICAL APPLICATION OF ELECTROMYOGRAPHY

by G. Weddell, B. Feinstein & R. E. Pattle, *Lancet*, **1**, 236, 20/2/43

When a wasted muscle is examined, a search is made for fibrillation and fasciculation, but only marked fibrillation can be seen, and even this is visible only in the superficial muscles in thin subjects. More exact information may be obtained by observations of the electrical activity of muscles. Recent progress in the study of the electrical behaviour of muscles in health and disease shows that many of the conclusions upon the presence or absence of fibrillation which have been based upon direct observation should be revised.

The present authors, working at a Military Hospital for Head Injuries and in the Departments of Anatomy and Orthopædic Surgery at Oxford, have done much to simplify the use of electromyography in clinical diagnosis, and they have confirmed many of the observations made previously on this subject by Denny-Brown & Pennybacker (1938). Their conclusions may be summarised as follows:

(i) When, more than three weeks after an injury, there is a sustained slight motor activity on attempted movement (even when the movement is not visible), and an absence of fibrillation potentials, it may be concluded that no axons have been cut and there is only a transient nerve block.

(ii) A mixture of fibrillation and motor unit action potentials means either a partial interruption or incomplete regeneration of the nerve. When there is doubt about the presence of fibrillation, a novocaine nerve block will stop the motor unit activity and so simplify the record.

(iii) When there are fibrillation action potentials without motor unit activity, there is complete section of the lower motor neurone. When denervated muscle does not respond to ordinary galvanic stimuli, electromyography is particularly helpful in determining the true condition of the nerve.

(iv) A mixture of fibrillation action potentials and a peculiar form of discharge called by the authors "nascent" motor unit potentials, shows that innervation is returning to the muscle.

(v) When action potentials resembling those of fibrillation follow insertion of a needle electrode into a muscle which shows no motor unit activity, there is complete interruption of the nerve. This provoked fibrillation activity is found either before true fibrillation appears or after it has ceased, and also immediately before "nascent" action potentials appear. This increased irritability therefore adds information in the absence of fibrillation.

(vi) When there is no electrical activity at all in a muscle, more than a few weeks after an injury, complete replacement of the muscle by fibrous tissue has occurred.

These conclusions show how much extra information can be obtained by means of electromyography in most cases of peripheral nerve damage. The method which the authors used is a simple one—the insertion into the muscle of a concentric needle electrode made from a small hypodermic needle, and connected to a high-gain amplifier which activates a cathode ray oscillograph and a loud speaker. The low-pitched noise of the motor unit potential is easily differentiated from the sharp clicking of fibrillation, and the oscillograph records, of which an example is given, can also be interpreted with ease.

In a denervated muscle the amount of fibrillation varies directly with the temperature, and it can be found in every case of muscle wasting if the muscle is warmed. Experiments on animals show that the time of onset of fibrillation varies with the size of the animal—mouse 3½ days, rat 4, rabbit 6, monkey 8 and man 18 in comparable muscles. As the time is lengthened by thyroidectomy, it seems that this variation is due to the different metabolic rates of the animals. The authors, on the other hand, found no direct correlation between the degree of fibrillation and the speed of wasting, so that the theory that wasting is due to the over-activity which results from fibrillation in wasted muscle appears to be false.

The electromyogram is used clinically by inserting the needle electrode into two or three places in the belly of the muscle and observing the electrical activity directly. Thus an exact record can be obtained of the state of all the muscles in the affected region and their progress can be followed by re-examination from time to time. Also the state of different parts of the same muscle can be compared, and the authors describe a case where the method led to the correct diagnosis when only the distal half of a muscle was denervated. As such a delicate method of examination is available, the level of a spinal cord lesion can be checked by observing which muscles are showing evidence of lower motor neurone denervation—for instance the presence of fibrillation, diminished motor unit activity, or of "nascent" potentials in an intercostal muscle will give an exact localisation of the position of a thoracic cord lesion.

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BRITISH MEDICAL BULLETIN

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The object of this Bulletin is to provide a guide to medical science and thought in Britain, and it consists mainly of summaries of a representative selection of British papers on subjects of medical interest. Any material appearing in the Bulletin may be published without fee, but acknowledgment of the source, by addition of the initial letters BMB followed by the serial numbers of the items selected, would be appreciated.

SPECIAL CONTRIBUTION

RECENT ADVANCES IN BACTERIOLOGICAL METHODS

by J. C. CRUICKSHANK, M.B., CH.B., D.T.M., DIP. BACT.

Although there is a constant flow of contributions to our bacteriological knowledge, the most striking advances follow in the wake of some new development in technique. It is of interest, therefore, to consider some of the more important methods which have been described in recent years. An observer returning to the medical laboratory after an interval of a decade would note changes in two principal directions. He would be struck by the efficiency of the modern selective culture media for the isolation of bacteria. Further, he would find that the bacteriologist is no longer content to identify an organism as a particular bacterial species but, in dealing with many important groups, regards it as essential to carry the identification a stage further by determining the subgroup or type to which the strain belongs. These types, to which reference will be made later, are a stable character of the organisms, so that the typing methods make it possible to trace the migrations of a strain and frequently to detect the probable source of an infection or an epidemic.

Each of these lines of advance is well exemplified in the investigation of the intestinal pathogens. Many new culture media have been described for their isolation and, while there is little to choose between the best of these, it is clear that they are so vastly superior to media such as MacConkey or Endo agar that the latter may almost be regarded as obsolete for this purpose. In selectivity, satisfactory differentiation of colonies, and rapidity of growth, Leifson's medium, or some modification such as that of Hynes (1942), or S.S. (Salmonella-Shigella) agar, has proved outstanding for the isolation of organisms of the typhoid-paratyphoid, Salmonella, and dysentery groups. These media, which contain sodium desoxycholate, inhibit the growth of *Bact. coli* and Gram-positive bacteria. The bismuth-sulphite-iron medium of Wilson and Blair is still held in high regard for the isolation of organisms of the enteric group, especially *Bact. typhosum*. It is the routine in most laboratories to culture fæces and urine from suspected enteric cases directly on desoxycholate and bismuth-sulphite media, and also to sow a fairly heavy inoculum into a fluid enrichment medium such as tetrathionate broth, from which, after incubation, subculture is made, again on to one or both of the solid selective media. Extensive experience has shown that by this technique the pathogen will seldom escape detection in infective material.

With a series of fæcal specimens from dysentery cases inoculated in parallel on Hynes' medium and on MacConkey agar, twice the number of isolations of Flexner's and Sonne's bacilli were made on the former in acute cases and six times the number in convalescence. A tellurite-iron citrate-neutral red agar, with or without rosolic acid, has also proved valuable for the dysentery group (Wilson & Blair, 1941). The data obtained from such investigations have necessitated the revision of previous conceptions in respect to carrier rates, the duration of excretion of the organism in convalescence, and the control of chemotherapy.

In the Salmonella group the pioneer work of antigenic analysis by Kauffmann and Bruce-White has been followed up, and many new Salmonella types have been recognised. In this field, however, the most far-reaching discovery was the demonstration by Felix (1934) of the Vi or virulence antigen of the typhoid bacillus. This is a labile antigen, associated with full virulence of the organism, found in freshly isolated strains, but readily lost on subculture. It is reasonable to think that an effective antityphoid vaccine should be prepared from a typhoid strain possessing Vi antigen, and laboratory trials and, more recently, experiences in the field confirm that this is so. As heat and most of the antiseptics usually employed to preserve vaccines cause damage to the Vi antigen, Felix (1941) prepared a vaccine which was sterilised and preserved with alcohol. This vaccine has been shown to be safe and to produce a satisfactory response of Vi antibodies in inoculated subjects. Antityphoid serum for therapeutic use should also contain Vi antibodies. A further development of Felix's work was his discovery that the blood of typhoid carriers almost always contains Vi antibodies; the Vi agglutination test has thus become a valuable means of narrowing the field in the search for carriers, and the test is, moreover, independent of intermittency of excretion of typhoid bacilli (Felix, 1938).

In 1938 and subsequent years, Craigie & Yen (1938), who had been working with a bacteriophage which was specific in its lytic action on Vi strains of typhoid bacilli, reported that, by propagation of this phage on individual strains, they were able to produce Vi phages specific in their action on these particular strains. These specific phages could thus be used to identify the strains, and typing of typhoid bacilli became possible. Craigie described 18 types and subtypes to which a number of new ones have now been added. A fresh weapon was placed in the hands of the epidemiologist, and already there have come from Britain and America a number of fascinating accounts * of the way in which a strain of a certain phage-type responsible for an epidemic or a few scattered cases has been traced back to its ultimate source. The technique of phage-typing is a specialised one usually carried out in a central reference laboratory, but facilities for its performance should be available to all public health investigators.

In the bacteriological diagnosis of diphtheria it is now acknowledged that it is necessary to use a selective medium containing tellurite. The laboratory which relies, as in the past, solely on Löffler's serum is likely to miss some of the acute cases and to fail to detect the diphtheria baciilus in a large number of contacts, carriers and convalescents. The ideal tellurite medium would be easily prepared, would grow typical colonies of all diphtheria strains in 24 hours and would inhibit other organisms. Further, the microscopic morphology of the organisms would be readily recognisable. The perfect medium has not yet been devised, but of the various formulæ which approach it more or less closely, that of Hoyle (1941) is one of the most popular. This medium contains blood, lysed by saponin or other means, and is specially successful when prepared with a meat-extract base by a method which avoids excessive heating (Johnstone & Zinnemann, 1943). The good tellurite medium also permits easy identification, by differences in colony form, of the *gravis*, *intermedius* and *mitis* types of diphtheria bacilli, a differentiation confirmed by subculture into certain other media including starch, which is fermented only by the *gravis* type. These types, which all produce the same toxin, were first described by Anderson, Happold, McLeod & Thomson (1931), in Leeds, where the *gravis* type was always, and the *intermedius* type almost always, found to be virulent to guinea-pigs. These two types are associated as a rule in man with more severe infections than the *mitis* type, which may, however, also cause severe and even fatal infections. Typing of diphtheria bacilli has frequently assisted in the detection of carriers responsible for outbreaks and has already afforded valuable information concerning cross-infection in hospital wards. Typing data collected over long periods throughout the world promise ultimately to give a better understanding of the epidemiology of diphtheria and the long-term relations of the organism to the human herd.

Hæmolytic streptococcal infections in the past presented many problems to the investigator. Many of these are still unsolved, but the technical advances of the last 15 years (Ministry of Health, 1939) have made it possible to distinguish the findings which are significant. Streptococci isolated from swabs or infective material must first be shown to be true β-hæmolytic streptococci by the ability of a young fluid culture to lyse a suspension of horse erythrocytes. Organisms giving a positive soluble hæmolysin test may then be classified into one or other of the serological groups described by Lancefield. This test, performance of which presents no great difficulty, consists in extracting from the organisms by acid, or by Fuller's formamide method, a carbohydrate substance which gives a precipitation reaction in the presence of the appropriate group antiserum. Thirteen groups designated A to M are recognised and, while certain of the other groups are not without pathogenicity for man, the hæmolytic streptococci which are of major importance in human infections belong to group A. Group A organisms are, however, not infrequently found in the normal throat, and identification must be carried a step further. By means of agglutination tests with absorbed sera, technically rather more difficult than the grouping procedure, Griffith defined 23 types within

* [*see, for example, BMB* 70]

group A. New types are constantly being recognised, and certain types are found in frequent association with certain forms of infection, so that one may refer, for example, to a "common scarlet fever type."

Lancefield and Griffith may be said to have played the same role as an earlier bacteriologist of whom it was said that he shook the tree for his followers to pick up the apples. Their methods rapidly led to new discoveries. It was confirmed, as the clinician had already suspected, that the same hæmolytic streptococcus may give rise to various manifestations in a single community. The search for, and isolation of, carriers was put on a more rational basis. New information relating to cross-infections in surgical and fever wards became available. Nowhere was the value of the new techniques more strikingly shown than in the careful investigation into puerperal fever by the workers at *Queen Charlotte's Hospital* in London. Only by the typing method could it have been proved that endogenous infection, *i.e.* infection of the placental site by organisms already present in the genital passages at the commencement of labour, is almost negligible as a cause of puerperal fever, and that the important sources of infection are to be found in the attendants or other contacts, or more rarely in the upper respiratory passages of the patient herself.

It was natural to hope that some equally satisfactory classification might be possible in the staphylococcus group. *Staph. aureus* infections are important to the surgeon, and in skin conditions, especially in children, and it is being increasingly recognised that certain strains are responsible for a frequent form of bacterial food poisoning. In view of the ubiquity of staphylococci it is desirable that there should be some means of identifying pathogenic strains and, if possible, of typing them. The coagulase test (Medical Research Council, 1943), which depends on the ability of a strain to form a coagulum in human or rabbit plasma, is the most reliable of the suggested methods of identifying potentially pathogenic and toxigenic strains of *Staph. aureus*. Although typing of staphylococci has not so far given such spectacular results as that of streptococci, the method has proved of some value and will probably be developed. It was studied by Cowan (1939) who, by observing agglutination of suspensions by absorbed sera on a slide, was able to divide strains into three main types and a number of additional subtypes. In an investigation suggested by the isolation of staphylococci from the inside of surgeons' gloves after operations, he and his colleagues showed that carriage of the organism on the hands was related to chronic carriage of the same type in the nose. Attempts by Fisk (1942) to apply phage-susceptibility of staphylococci for purposes of identification are still in an experimental stage.

The present war, like the last one, has provided a stimulus to the study of the organisms of the gas-gangrene group. The best methods of using the existing techniques have been studied and defined (Medical Research Council, 1943). The examination of anærobic bacteria on a large scale has been hampered by the need of special apparatus, and it is of interest to note the development of methods of growing these organisms in the presence of air. This may be done by adding to fluid media, which must be heated immediately before use, 0·1 to 0·2% of agar and certain reducing substances such as ascorbic or thioglycollic acid. Vigorous growth of anærobes can also be obtained in ordinary broth or peptone water by the addition of a small strip of sheet-iron.* Characteristic changes produced in certain of the iron media provide additional means of bacterial identification.

The overcrowding which occurs in time of war also stimulates research on airborne infections, at any time a matter of high importance owing to the extreme difficulty of controlling such disease. The accurate sampling of bacteria in the air presents a considerable problem, since the older method of exposing open plates of culture media for a prolonged period resulted in the selective capture of the heavier dust particles. This has been overcome by the slit-sampler devised by Bourdillon, Lidwell & Thomas (1941). Air is drawn through a slit by means of a vacuum pump and made to impinge on a rotating plate of culture medium, if necessary a medium containing gentian violet which will permit the selective growth of streptococci indicative of respiratory pollution. The collection of data from samples thus obtained during short periods under different conditions has put these studies on a new footing and made possible the adequate control of experimental work on aerial disinfection by hypochlorites, hexyl-resorcinol, propylene-glycol and other agents.

The amazing discoveries in the sphere of chemotherapy have been a close concern of the bacteriologist, who has himself not been idle in the search for substances with bactericidal or bacteriostatic action. Penicillin, which may prove, when the problem of production in adequate quantity is solved, to be one of the most valuable of these agents, is the discovery of a bacteriologist, and other substances extracted from bacteria and fungi are constantly being investigated (Waksman, 1941).

The widespread use of the drugs of the sulphonamide group has caused the bacteriologist to modify certain of his methods. He now frequently receives blood or other material for culture containing a sufficiently high concentration of the drug to inhibit growth of the organisms *in vitro*. To counteract this, para-aminobenzoic acid is added to the culture medium; this substance, which is an essential growth factor for many organisms, is utilised by means of an enzyme, the action of which would otherwise be diverted by the chemically similar sulphonamide.

The methods noted above are some of those which are already yielding results of practical importance in the diagnosis and control of disease. The past few years have also seen the appearance of apparatus of great interest to workers in various branches of science which will undoubtedly further our theoretical knowledge of bacteriology and immunology. The electron microscope which extends resolving power to a present potential limit of about 50 Ångström units has already given new information concerning the morphology of bacteria and viruses, and the character and thickness of films of antibody on sensitised bacteria. It is probable also that the study of viruses, phages and antibody complexes will be greatly advanced by the use of the new high-speed centrifuges, the largest of which, the Svedberg centrifuge, runs at speeds up to 65,000 revolutions per minute.

* [*See also BMB* 147]

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[*As space does not permit mention of all the important papers on the subjects discussed, reference has been given to a few selected papers or reviews in which the methods are described.*]

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[1] [*Typescript abstract available on request*]

[2] [*See BMB* 76]

Dr. J. C. Cruickshank was a member of the West African Medical Staff in Gambia for a number of years before becoming Lecturer in Bacteriology at the London School of Hygiene and Tropical Medicine. He is at present in charge of the Exeter laboratory of the Emergency Public Health Laboratory Service [*which is described in BMB* 64].

At the School of Hygiene Dr. Cruickshank was one of a team engaged in the isolation of immunising fractions from bacteria by chemical means. Fractions effective in the prophylaxis of the infection in mice were obtained from the whooping-cough bacillus (with G. G. Freeman). His published work includes papers on the so-called Bacterium typhi flavum, on certain antigenic components of the Salmonellas, and the chemotherapy of experimental pertussis and anthrax infections.

BACTERIOLOGICAL METHODS AND THEIR APPLICATION

A SIMPLE "CHOCOLATE"-STARCH MEDIUM FOR THE RAPID TYPE DIFFERENTIATION OF *C. DIPHTHERIÆ*

by R. Hodgson, R. M. Heggie & P. L. Sutherland, *Journal of Pathology & Bacteriology*, **55**, 199–204, April 1943

The epidemiological value of differentiating the types of diphtheria bacilli is now widely recognised. A provisional opinion in respect to the type can usually be given from the colonial appearance on the primary culture-plate on which the swab was inoculated, and the type is finally established by subculture into other media, including starch and broth tubes. The present workers, from the Public Health Laboratory of Wakefield, England, have devised a method for the simpler and more rapid identification of diphtheria types by subculture from the primary plate to a single solid medium, the result being obtained from the appearances on this medium after 24 hours' incubation.

Three stock solutions are required: (*a*) 2 % starch solution, sterilised by autoclaving; (*b*) 1 % cystine solution, as used in Clauberg's medium, boiled immediately before use; (*c*) 2 % nutrient agar. To 100 ml. of melted agar, cooled to 60° C., add 10 ml. of horse blood. Mix and place in a water-bath at 75° C. for 10 minutes. Cool to 50° C. and add the following, mixing well after each addition: 1 ml. of cystine solution, 20 ml. of horse serum, 15 ml. of starch solution. Pour plates fairly thickly. It is advisable to store the blood and serum in the ice-chest for some days before use, to overcome the possibility that the diastase in these substances may cause hydrolysis of the starch. It is to be noted that the medium is not a selective one suitable for primary culture.

Colonies from the primary plate are spread over a square centimetre of the medium, as many as 12 cultures being seeded on to a single plate. After 24 hours' incubation, cultures of *intermedius* type are easily recognisable by the appearance described by the Leeds workers, Gordon & Higginbottom (1942). They present a fine growth with a tendency to form individual colonies, and produce a definite dull greenish discoloration in the medium. The plates are then flooded with Jensen's iodine (1 % iodine in 2 % potassium iodide), the excess being drained off after a few seconds. Two minutes later, identification of *gravis* and *mitis* growths can be made. The *gravis* cultures, which were creamy white, opaque and confluent, with a dryish appearance in reflected light, are now bright yellow and surrounded by a distinct halo, the medium immediately below and around the growth being transparent against the dark chocolate colour of the rest of the medium. These appearances were originally described by Anderson *et al.* of Leeds University (1931). *Gravis* cultures tend later to flake off from the medium. *Mitis* growths, which were also creamy white but less dense and more glistening than those of *gravis* type, become yellowish-green on treatment with the iodine, but have no halo. Subcultures may still be made after addition of the iodine.

With 120 strains examined by this method, and by the usual biochemical reactions, there was agreement as to type in 118, the remaining two strains, which gave a *mitis* type of growth, being non-starch-fermenting strains of atypical character.

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[1] [*see BMB* **32**]

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SLIDE CULTURE METHOD FOR TUBERCLE BACILLI

by K. S. Rosenberg, *Lancet*, **1**, 615–616, 15/5/43

Tubercle bacilli are unlikely to be found in direct films of tuberculous material unless it contains at least 10^5 organisms per cm³. Culture on Loewenstein's medium can detect bacilli in material containing as few as 10 organisms per cm³., but the result is probably not available for 3 weeks. With t e me lo w deser ed in a week with material containing 10^3–10^5 tubercle bacilli per cm³.

The principle of the method, originally described by Pryce (1941) working with the *Emergency Medical Service* at an English sanatorium, consists in treating with acid a film of the material spread on a slide. Contaminating organisms having thus been destroyed, the film is washed, immersed in a suitable fluid culture medium, and incubated. The present worker, at another sanatorium in the same *Service*, uses as culture medium Kirchner's serum-salt mixture. This consists of equal parts of normal human serum and a synthetic medium: di-sodium orthophosphate 3 g.; mono-potassium orthophosphate 4 g.; magnesium sulphate 0·6 g.; asparagin 2·5 g.; glycerol 20 cm³.; distilled water to 1 litre.

Further modifications of the method have been made, the author's technique being as follows. One-ounce [about 28 cm³.] bottles with perforated screw-caps and rubber washers are filled with water and autoclaved. The suspected material is spread on microscopic slides which have been divided longitudinally. After drying in the incubator, the films are treated with 6 % H_2SO_4 for 45 minutes in a sterile staining rack with a glass lid. Two slides are then placed back to back in the bottles of water for 10 minutes. A needle attached to a water-pump is thrust through the cap, and the water is withdrawn and replaced by culture medium. The bottles are incubated for one week, then the slides are stained by Ziehl-Neelsen's method. Where tubercle bacilli have grown, the clumps are usually visible with the low power of the microscope.

Of a series of sputa positive by direct examination, 95 % showed a visible growth in 6 days. Of 105 sputa negative by direct examination, 11 showed good growth, 3 showed isolated bacilli, and 3 were contaminated. If non-purulent sputa, none of which were positive by any method, are disregarded, the positive findings by the slide-culture method in this series rise from 14 % to 24 %. The tubercle bacilli in this trial were all of human type.

There is thus evidence that this simple and inexpensive procedure is valuable for the detection of tubercle bacilli within a week in a considerable proportion of sputa negative on direct examination.

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[1] [*typescript abstract available on request*]

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IRON MEDIA FOR CULTIVATION OF ANÆROBIC BACTERIA IN AIR

by N. J. Hayward & A. A. Miles, *Lancet*, **1**, 645–646, 22/5/43

The adequate study of anærobic bacteria is often hampered by the scarcity of anærobic jars. Certain culture media of high reducing intensity, such as thioglycollate-agar-broth, permit the growth of these organisms under ærobic conditions, but there is need for a more stable and easily prepared agent. Spray (1936) suggested the use of a strip of iron and the present authors, working in the Department of Bacteriology of *University College* Medical School, London, where Miles is Professor of Bacteriology, have extended the method.

The fluid media, peptone water, "sugar" media or milk, preferably in narrow test-tubes, are heated in a boiling water-bath to drive off the air, and cooled quickly. Strips of sheet iron (no. 26 gauge, measuring 3 × 25 mm.) are dropped into each tube. The strips, which are sterilised by flaming immediately before use, or dry-sterilised and stored in screw-capped bottles, can be recovered and used repeatedly. They were found more effective than iron filings.

On incubation a precipitate appears on the iron and at the bottom of the tube. Certain anærobes produce blackening of the iron and the medium is darkened. If a fermentable sugar is present, the acid produced prevents this blackening. These appearances may give additional aid in the identification of bacterial species.

Peptone water containing the strip was converted into a medium which induced vigorous growth from small inocula of the most fastidious anærobes, including *Cl. tetani* and *Cl. œdematiens*. The species tested included numerous strains of 11 species of Clostridia, and strains of *Fusiformis*

and anærobic streptococci. All grew well and their fermentation reactions, tested in iron-peptone-water sugar media, were found correct.

REFERENCE
Spray, R. S. (1936), *J. Bact.*, **32**, 135

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SLIDE-TEST FOR COAGULASE-POSITIVE STAPHYLOCOCCI

by B. Cadness-Graves, R. Williams, G. J. Harper & A. A. Miles, *Lancet*, **1**, 736–738, 12/6/43

The most reliable laboratory test for the identification of potentially pathogenic strains of *Staph. aureus* is the coagulase test. This test, which may take 24 hours, depends on the property of these strains to coagulate citrated plasma. It has been suggested that these coagulase-positive potentially pathogenic strains be called *Staph. pyogenes* (Cruickshank, 1937). It had previously been noted by Much (1908) and by Birch-Hirschfeld (1934) that coagulase-positive cocci were rapidly clumped when suspended in plasma. If this occurred with all coagulase-positive strains and did not occur with other cocci, much time would be saved, since the clumping test occupies only a few seconds. The present workers report the results of a study of the correlation between the coagulase and the clumping tests. Dr. Cadness-Graves is a pathologist to the *Emergency Medical Service*, Miles is Professor of Bacteriology at *University College* (London), and the other two workers belong to a *Medical Research Council* Unit at Birmingham Accident Hospital.

In the first series of tests, made by one practised observer on 442 strains of staphylococci from various sources, there was agreement between the tests with 440 strains, of which 280 were positive and 160 negative. The remaining two strains gave a feebly positive coagulase test and a negative clumping test. No clumping occurred with any of the other common bacteria tested. A solution of fibrinogen could be used in place of plasma for either test.

In a second series, observations were made by three workers on 860 strains, 558 of which gave a positive coagulase test. A record was made of the rapidity of clumping, from which it was clear that late or doubtful clumping appearing after 20 seconds was not a reliable indicator of *Staph. pyogenes*. Regarding these strains as negative, a positive clumping test was found to indicate 87 % of strains of *Staph. pyogenes*. Coagulase-negative strains do not give a positive clumping test. The authors suggest that, with increased experience, results as clear-cut as those in the first series would be obtained.

The recommended technique for the rapid test is as follows: A small drop of water is placed on each of two slides with a loop of 2 mm. diameter. The colony to be tested is rubbed carefully into one drop so as to make a homogeneous *dense* suspension. A small quantity is transferred to the drop on the other slide to make a film. A 1-mm. loop of fresh human plasma is mixed rapidly with the suspension on the first slide. If clumping occurs within 10 seconds, a presumptive diagnosis of *Staph. pyogenes* may be made, confirmed by the appearance of the stained smear. If no clumping occurs, and the stained smear shows gram-positive cocci, a tube of broth is inoculated for a coagulase test by one of the accepted techniques. Though late clumping is suggestive, it must not be used as a basis of identification.

It is estimated that the use of this rapid method will reduce the number of coagulase tests required by about 40 %.

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TYPING OF PARATYPHOID B BACILLI BY MEANS OF Vi BACTERIOPHAGE: A Report to the Medical Research Council

by A. Felix & B. R. Callow, *British Medical Journal*, **2**, 127–130, 31/7/43

The typing of typhoid bacilli by means of specific Vi bacteriophages has provided the epidemiologist with a valuable method of tracing the source of infections.[1] The authors, working with the *Emergency Public Health Laboratory Service*, now show in the present paper, which is a Report to the *Medical Research Council*, that the same technique may be applied to the study of paratyphoid B.

Felix had previously shown that *Bact. paratyphosum* B has a heat-labile Vi antigen similar in nature to that of the typhoid bacillus, and all of the many strains examined in the course of the work reported here possessed this antigen. The phages encountered in the early part of the investigation proved to be O-phages, active against the O or somatic antigen of the bacillus. These phages, which lysed all strains of *Bact. paratyphosum* B and also those Salmonellas possessing the same O antigen, could not be induced to become specific for any particular strain.

Ultimately Vi phages were obtained and it was found that paratyphoid B strains were either lysed by all of these phages or were resistant to all phages. No further progress was made until the occurrence of a small outbreak at Ipswich. It was found possible to adapt one of the original Vi phages which was then able to lyse the previously resistant Ipswich strains. The original Vi phage was known as type 1, the new one as type 2, and a later type, adapted in the same way, as type 3a. Type 2 and type 3a phages are able to lyse type 1 bacilli as well as their own specific type. Another subtype, 3b, was later discovered. Strains of paratyphoid B bacilli which cannot be typed with any of the four Vi-phages are said to belong to group Z. Only 7 % of 714 strains could not be typed. This is in contrast to the work on the typhoid bacillus, in which Felix used 22 Vi phages and found 15·9 % of strains untypable.

As with the typhoid bacillus, carriers repeatedly examined are always found to carry the same type of organism, and cases infected from a single source are found to be excreting the same type.

The remainder of the paper gives an outline of the types of *Bact. paratyphosum* B found in the outbreaks in Great Britain in recent years. Large epidemics occurred in 1941 and these were all due to type 1.

[1 see *B.M.B.* 64, 69 & 70 for accounts of this method of typing typhoid bacilli.]

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A NOTE ON THE VALUE OF PHAGE TYPING IN THE INVESTIGATION OF AN OUTBREAK OF PARATYPHOID B FEVER

by J. R. Hutchinson, *British Medical Journal*, **2**, 130, 31/7/43

The author, who is an epidemiologist of the British Ministry of Health, gives the first account of the use in the field of the bacteriophage method of typing paratyphoid B bacilli. Twelve cases were reported over a short period in the town of Ipswich. Ten of these were excreting type 2 and the other two type 1 bacilli. All the persons infected with type 2 organisms obtained confectionery from one shop, in which the source of infection was found in the person of an unattended case. The two excreters of type 1 bacilli had no dealings with this shop. Other cases which had occurred in the rural districts outside Ipswich fitted into the same picture, all those infected with type 2 bacilli being customers of the shop in question, and the excreters of type 1 bacilli having no contact with this source.

The complete agreement between the bacteriological and epidemiological findings thus illustrates the way in which the method is likely to prove of great value to the investigator.

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TYPHUS RICKETTSIAL AGGLUTINATION TESTS IN THE MIDDLE EAST FORCES AND EGYPT

by C. E. van Rooyen & W. G. C. Bearcroft, *Edinburgh Medical Journal*, **50**, 257–272, May 1943

The Weil-Felix reaction has been of great practical value in the laboratory diagnosis of the typhus group of fevers; but, although the results of agglutination of different O strains of *B. proteus* by the sera of patients suffering from rickettsial infections indicates differences in the causal organisms, the diseases within the group cannot be clearly differentiated by the Weil-Felix reaction. Now that modern techniques enable relatively pure suspensions of rickettsiæ to be prepared in the laboratory, the use of such suspensions in serological tests has already extended our knowledge of the relationship of the various types of human rickettsial infections to each other.

In this paper, the authors review the recent terature on this subject and publish their own observations on the sera of typhus cases encountered in the Middle East. They used five antigens in each test; three of the antigens were the standard Proteus OX_{19}, OX_2 and OXK suspensions and the other two were pure suspensions of epidemic and murine strains of typhus rickettsiae which had been prepared by Dr. James Craigie of Toronto University. Sera were examined from 23 cases of typhus among civilians in Egypt (Cairo and Tanta), and from 50 cases among British and Allied troops in Palestine, Syria, Iraq and Egypt, while the sera of 100 healthy persons and of 74 cases of other infections were examined as controls.

The results are set out in tabular form. There was close correlation between the results of the Weil-Felix and rickettsial agglutination tests. None of the sera from normal individuals or from patients suffering from diseases other than typhus gave false positive results with the rickettsial suspensions. Although the rickettsial agglutination reactions were not so easy to read as those of the Weil-Felix tests they served to distinguish between louse-borne epidemic typhus and the flea-borne murine type of infection. With the sera from cases of the epidemic disease, cross-agglutination to low titre occurred with the suspensions of murine rickettsiae, the ratio of titres with the homologous to the heterologous rickettsiae being approximately 3 to 1; in the case of murine typhus the corresponding ratio was roughly 10 to 1.

The incidence of typhus during 1942 was not high in the Middle East but the epidemic form tended to occur in Cairo, in the winter months, among the civil population. The murine form was more frequently met with among the troops, and the cases in Syria, Palestine and the Suez Canal Zone tended to be of this type.

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CANCER AND RADIOTHERAPY

SELECTED PAPERS FROM THE *ROYAL CANCER HOSPITAL (FREE)* AND THE *CHESTER BEATTY RESEARCH INSTITUTE*, Volume I, 1935–1939, London:

I. THE PROBLEM OF THE SURGICAL TREATMENT OF CANCER OF THE RECTUM, by W. E. Miles (1939), *Amer. J. Surg.*, **46**, 26–39; II. THE PATHOLOGY, DIAGNOSIS, AND TREATMENT OF HASHIMOTO'S DISEASE (STRUMA LYMPHOMATOSA), by C. A. Joll (1939), *Brit. J. Surg.*, **27**, 351–389; III. A CLINICO-PATHOLOGICAL CLASSIFICATION OF CANCER OF THE BREAST, by R. W. Raven (1939), *Brit. med. J.*, **1**, 611–616; IV. MULTIPLE METASTATIC TUMOURS IN THE BRAIN ARISING FROM PRIMARY BRONCHIAL CARCINOMA, by W. E. C. Dickson & C. Worster-Drought (1936), *J. Neurol. Psychopath.*, **16**, 289–320; V. MULTIPLE MENINGEAL AND PERINEURAL TUMOURS WITH ANALOGOUS CHANGES IN THE GLIA AND EPENDYMA (NEUROFIBROBLASTOMATOSIS), by C. Worster-Drought, W. E. C. Dickson & W. H. McMenemey (1937), *Brain*, **60**, 85–117; VI. THE SIGNIFICANCE OF THE RÖNTGEN, by W. V. Mayneord (1937), *Acta of the Internat. Union against Cancer*, **2**, 271–282; VII. THE USE OF X-RAYS AND GAMMA RAYS IN MEDICINE, by W. V. Mayneord (1939), *Reports on Progress in Physics*, **5**, 284–301; VIII. THE "QUALITY" OF HIGH VOLTAGE RADIATIONS—**1.**, by W. V. Mayneord & J. E. Roberts (1935), *Brit. J. Radiol.*, **8**, 341–364; IX. THE "QUALITY" OF HIGH VOLTAGE RADIATIONS—**2.**, by J. R. Clarkson & W. V. Mayneord (1939), *Brit. J. Radiol.*, **12**, 168–180; X. MEASUREMENTS OF LOW-VOLTAGE X-RAYS (CHAOUL TECHNIQUE), by W. V. Mayneord (1936), *Brit. J. Radiol.*, **9**, 215–237; XI. ON DEPTH DOSES FROM TELERADIUM UNITS, by W. V. Mayneord & J. Honeyburne (1938), *Brit. J. Radiol.*, **11**, 741–754; XII. A PRELIMINARY NOTE ON LOW-VOLTAGE X-RAY THERAPY, by J. M. W. Morison, D. Hugo & W. V. Mayneord (1935), *Brit. med. J.*, **2**, 783–788; XIII. SHORT-DISTANCE LOW-VOLTAGE X-RAY THERAPY, by P. A. Flood & D. W. Smithers (1939), *Brit. J. Radiol.*, **12**, 462–485; XIV. THE RAPID PRODUCTION OF TUMOURS BY TWO NEW HYDROCARBONS, by W. E. Bachmann, E. L. Kennaway & N. M. Kennaway (1938), *Yale J. Biol. Med.*, **11**, 97–102; XV. EXPERIMENTS ON THE CHEMOTHERAPY OF CANCER: 2.—THE EFFECT OF ALDEHYDES AND GLUCOSIDES, by E. oy · . . , . ·, , ~ , XVI. EXPERIMENTS ON THE CHEMOTHERAPY OF CANCER: 3.—THE INDEPENDENCE OF TISSUE RESPIRATION AND GLYCOLYSIS AND THE GROWTH RATE OF TUMOURS, by E. Boyland & M. E. Boyland (1939), *Biochem. J.*, **33**, 618–621; XVII. GALL STONES AND CANCER: A PROBLEM OF AETIOLOGY WITH SPECIAL REFERENCE TO THE ROLE OF IRRITATION, by H. Burrows (1939), *Brit. J. Surg.*, **27**, 166–168; XVIII. CHEMICAL COMPOUNDS AS CARCINOGENIC AGENTS, by J. W. Cook, G. A. D. Haslewood, C. L. Hewett, I. Hieger, E. L. Kennaway & W. V. Mayneord (1937), *Amer. J. Cancer*, **29**, 219–259; XIX. CHEMICAL COMPOUNDS AS CARCINOGENIC AGENTS: FIRST SUPPLEMENTARY REPORT:—LITERATURE OF 1937, by J. W. Cook & E. L. Kennaway (1938), *Amer. J. Cancer*, **33**, 50–97; XX. PHOTO-OXIDES OF CARCINOGENIC HYDROCARBONS, by J. W. Cook, R. Martin & E. M. F. Roe (1939), *Nature*, **143**, 1020–1021; XXI. THE INFLUENCE OF CARCINOGENIC COMPOUNDS AND RELATED SUBSTANCES ON THE RATE OF GROWTH OF SPONTANEOUS TUMOURS OF THE MOUSE, by A. Haddow (1938), *J. Path. Bact.*, **47**, 567–579; XXII. THE INFLUENCE OF CARCINOGENIC SUBSTANCES ON SARCOMATA INDUCED BY THE SAME AND OTHER COMPOUNDS, by A. Haddow (1938), *J. Path. Bact.*, **47**, 581–591; XXIII. THE BIOLOGICAL CHARACTERS OF SPONTANEOUS TUMOURS OF THE MOUSE, WITH SPECIAL REFERENCE TO RATE OF GROWTH, by A. Haddow (1938), *J. Path. Bact.*, **47**, 553–565; XXIV. CELLULAR INHIBITION AND THE ORIGIN OF CANCER, by A. Haddow (1938), *Acta of the Internat. Union against Cancer*, **3**, 342–353; XXV. THE ASSOCIATION OF CARCINOGENICITY AND GROWTH-INHIBITORY POWER IN THE POLYCYCLIC HYDROCARBONS AND OTHER SUBSTANCES, by A. Haddow & A. M. ROBINSON (1939), *Proc. roy. Soc. B.*, **127**, 277–287; XXVI. THE RELATIVE POTENCY OF CARCINOGENIC COMPOUNDS, by J. Iball (1939), *Amer. J. Cancer*, **35**, 188–190; XXVII. BILE PRODUCTION IN TUMOUR-BEARING MICE AND THE USE OF BILE IN FILTRATION, by L. D. PARSONS (1939), *Nature*, **144**, 75–76; XXVIII. CHANGES IN THE LYMPH GLANDS OF TUMOUR-BEARING MICE, by L. D. Parsons (1938), *J. Path. Bact.*, **47**, 501–523; XXIX. THE ACTION OF SOME *ENDO*SUCCINIC ACIDS DERIVED FROM POLYCYCLIC HYDROCARBONS ON THE RED BLOOD CORPUSCLES OF THE MOUSE, by F. L. Warren (1939), *Biochem. J.*, **33**, 165–169; XXX. ESTIMATIONS OF IRON IN THE LYMPH GLANDS OF MICE DURING TREATMENT WITH A CARCINOGENIC COMPOUND, by F. L. Warren (1939), *Biochem. J.*, **33**, 729–733.

[*These Papers, now collected together in one bound volume, have been selected for their outstanding interest from those published in various journals by members of the Staff of the Royal Cancer Hospital (Free) during the years* 1935 *to* 1939.

They are concerned partly with clinical aspects, partly with physical problems of determining the dose of radiation needed for the successful treatment of malignant disease, and partly with work on experimental carcinogenesis.

The following is a composite review by three different writers. It has been divided into Clinical, Physical and Experimental Sections.]

A. *CLINICAL*

I. This paper opens with a discussion of the method of spread of cancer of the rectum. There are three distinct paths:

(i) by direct extension through continuity of tissue,
(ii) through the venous system,
(iii) through the lymphatic system.

Spread by the lymphatic system is much the most important, and to deal with this satisfactorily an abdomino-perineal operation is needed.

The one-stage abdomino-perineal operation practised by the author is described in detail with great clarity. The preparation of the patient receives attention and the importance of following exactly the instructions given is stressed. The technique of the operation is given under three headings: the abdominal, pelvic, and perineal portions. The position of the incision and the exposure are mentioned and then the actual operative procedure is divided into seven stages, with each stage so described that they can be followed exactly, from the first examination of the pelvic colon to the

completion of the operation by the removal of the isolated bowel and the opening of the proximal end of the pelvic colon. In conclusion, the author describes the methods of dressing and after-treatment.

II. This condition, about which there is considerable confusion, is clearly distinguished from other types of thyroid disease or neoplasia and it is pointed out that Hashimoto's name " Struma lymphomatosa " is undoubtedly correct. The condition with which it is most often confused, Riedel's Disease, is also described and numerous coloured illustrations bring out the difference between the two.

While it is true that the pathogenesis and ætiology are obscure, the clinical findings, together with the histological appearances, are sufficiently characteristic for diagnosis of the condition. The differential diagnosis by clinical signs and symptoms may be difficult. Length of history and size and type of goitre are important, and pressure effects and the presence or absence of myxœdema or hyperthyroidism must be looked for.

Treatment may be surgical for the relief of pressure symptoms, but probably radio-therapy will do all that is necessary. The prognosis in treated cases is good, but the possibility that myxœdema will supervene must be kept in mind.

III. The author proposes a new classification of carcinoma of the breast, founded on both clinical and pathological findings.

IV. The difficulty of distinguishing between metastases from bronchiogenic carcinoma and primary brain tumours remains very great, but increasing knowledge of the behaviour of carcinoma of the lung shows that this syndrome is not uncommon. Three types of cases have produced it:

(i) sclerosing bronchial carcinoma,
(ii) small growths in relation to the secondary bronchus,
(iii) massive primary in the periphery of the lung.

Such cases are illustrated by numerous photographs and photomicrographs. Metastases are found most often in the temporo-sphenoidal and frontal lobes, in the cerebellum, and also in the choroid plexuses, where their appearance may lead to an erroneous diagnosis of malignant papilloma of the choroid.

V. Two cases of this rare condition are fully described. Both ended fatally and, at *post mortem*, multiple tumours were found in the central nervous system and some on the peripheral nerves. Histologically, the tumours varied from meningioma to neurofibroma. The condition is described as neurofibroblastomatosis.

It is believed that this, like other multiple tumour syndromes, is due to a disturbance in the action of the evocators which stimulate and regulate the growth of tissues and organs. The authors advance certain theories as to the possible means by which perversion of the evocation fields at an early stage in embryonic life may result in multiple neoplasia.

B. *PHYSICAL*

VI. Calculations of the effective Atomic Numbers and X-ray absorption coefficients of a large number of biologically important substances, including carbohydrates and proteins, show that they will differ from air in their X-ray energy absorption. On the whole it may be said that the energy absorbed by soft tissues will be within 10 % or 15 % of that absorbed by air for wavelengths greater than 0·2Å: for shorter rays the agreement will be much closer. In the case of certain substances such as thyroxine, the absorption coefficient is high, but as these substances are present only in small amounts, the total effect is not more than a 7 % increase in energy absorption. Thus it is shown that the *roentgen* (for which a revised definition is proposed) is a very suitable unit for the measurement of short wave electromagnetic radiations, but warning is given that it would be unwise to deduce from the dose in *roentgens* the energy absorption in special regions.

The variation of radiation " quality " within a mass of tissues is described.

VII. Possible methods of dosage measurement are reviewed and the measurement, in terms of the most suitable unit (namely the *roentgen*) for X and gamma rays, by means of the parallel-plate chamber and of small enclosed chambers, described and discussed. The relationship between *roentgens* and the energy absorbed in human tissue is surveyed as in the preceding paper.

The production and uses of Isodose Curves are described and the reasons for the present trend towards higher voltage X-rays are discussed.

A survey of the methods of using radium therapeutically is made, with special reference to the many mathematical studies of source distribution. The radium " bomb " is described and a typical dose distribution is shown.

VIII. Of the three methods of " quality " specification, viz., the Equivalent Constant Potential, the Equivalent Wavelength, and the Half-Value Layer, the last is shown to be the most suitable for heterogeneous beams. The measurement of the absorption coefficients of certain light elements is suggested as a possible alternative.

The suitability of different metals as filter materials is investigated by spectrographic and ionisation measurements, and tin is shown to be superior to lead or copper for the 200–400 kv. range. Of various combinations of metals tried only a tin-tantallum filter showed any improvement over tin, whilst barium-copper has possibilities.

Tin is also considered to be the best material for Half-Value Layer measurements in the 200–400 kv. range.

IX. Two methods, one depending on the differential increase in photo-electric emission from the walls of metal and carbon ionisation chambers with increasing wavelength, and the other on the variation, with wavelength, of absorption in copper, are used to explore changes in " effective wavelength " of X-radiation within a scattering medium. Reasons for the final preference for the former method are given.

The effective wavelength increases with the field size and depth. At a depth, the value from 350 kv. primary radiation may be less than that for primary 250 kv. radiation.

A reduction in wavelength of the primary radiation alone is found with depth. The amounts of primary and secondary radiation at different depths are measured: the maximum amount of scattered radiation is reached at between 2 and 5 cm. deep; scatter may contribute up to 80 % of the dose at about 15 cm. deep.

The bearing of these results on the question of the relative biological effect of different X-ray wavelengths is emphasised.

X. Measurements of X-rays from the Siemens 60 kv. set, by means of a special dosage-rate meter employing a Lindemann electrometer and a very small chamber, are described. At 5 cm. focal skin distance the tube output is about 25 *r* per minute per milliampere, and the radiation has an average wavelength of about 0·32Å.

Percentage backscatter on the surface, percentage depth dose values and complete radiation distributions are given for a variety of fields. The small amount of radiation outside the geometric confines of the beam, and the considerable variation between centre and edge doses, are noted. Measurements of stray radiation around the tube are quoted.

XI. Using an experimental teleradium unit, the effects of variation of focal skin distance, filter thickness, and area of source, on dosage, have been investigated. The amount of soft radiation at the aperture increases with focal skin distance as does the percentage depth dose. A filter of 0·5 mm. lead plus 0·6 mm. brass gives the maximum depth dose improvement. For short (2–3 cm.) focal skin distance, increase in source area improves the percentage depth dose by some 20 %. No such change occurs for long (10 cm.) focal skin distance.

The depth dose cannot be accurately calculated by inverse square law alone. The effect of an apparent absorption coefficient of 0·025 $cm.^{-1}$ must be included for heavily filtered sources.

XII. An account is given of the first use of short distance low-voltage X-ray therapy in Britain, with a description of the methods used by Chaoul, the originator of this particular type of plant and the pioneer of this method of treatment.

The first 40 cases treated at the *Royal Cancer Hospital* are discussed.

XIII. The apparatus developed by Chaoul and Adam has been used in the treatment of 310 malignant and 190 non-malignant cases. Treatment by this method is now usually described as Contact Therapy.

For treatment to be successful, the lesion must be accessible and of reasonable depth. The tumour dose to be delivered in the time planned must be predetermined, and the volume treated must more than include the clinical limits of the tumour. Treatment may be by single or multiple fields and various arrangements are shown with photographs of

the tumours treated. The distribution of dosage is illustrated with various ingenious contrivances used in treatment. Tables show a high percentage of good results.

The Philips " Metalix " short distance low-voltage X-ray therapy apparatus is also described and a diagram is given.

C. *EXPERIMENTAL*

[Experimental Carcinogenesis, an outcome of the study of occupational cancer in man, became established as an essential weapon in the study of the cancer problem when, in 1915, Yamagiwa and Itchikawa succeeded in inducing tumours of the skin in rabbits by repeated applications of coal-tar. The full utilisation of this new technique depended, however, on the isolation and identification of the constituents of tar responsible for this action. The way in which this was achieved, by a fruitful collaboration between physicists, chemists and pathologists at the Research Institute of the *Royal Cancer Hospital*, under the leadership of Prof. E. L. Kennaway, represents one of the most fascinating chapters in modern cancer research. The adaptation, by Mayneord and Hieger, of fluorescence spectrography as a means of recognising carcinogenic fractions in tar, led to the isolation, from some 2 tons of pitch, of a few grammes of a highly carcinogenic crystalline product, which was subsequently identified by Cook and Hewett as the polycyclic hydrocarbon, 3 : 4-benzpyrene. The synthesis of several hundred related compounds, of widely varying carcinogenic potency, followed in due course, partly as an attempt to correlate chemical structure and carcinogenicity, and partly to investigate any possible relationship between these compounds and the sterols. In this development of the subject, the Research Institute of the *Royal Cancer Hospital* (subsequently constituted as the *Chester Beatty Research Institute*) continued to play a leading part.]

There are 17 papers on subjects connected with experimental cancer research. These include 2 reviews of the literature on chemical compounds as carcinogenic agents (XVIII, XIX), 5 publications on the inhibitory action of carcinogens on tumour growth (XXI–XXV), 4 on carcinogenesis by hydrocarbons and other agents (XIV, XVII, XX, XXVI), and 6 on various other aspects of the cancer problem (XV, XVI, XXVII–XXX).

In XVIII and XIX considerable space is devoted to the relationship between the chemical structure of polycyclic hydrocarbons and their carcinogenic potencies, while due attention is also given to such biological considerations as the mechanism of carcinogenesis; local, systemic, and genetic factors influencing carcinogenesis; and the systemic effects of carcinogens on normal and neoplastic tissues. Brief sections on histology and cytology, tissue culture, and viruses, in relation to carcinogenesis, complete the reviews. The scope of these reviews is wide, the bibliography (which includes 374 references) is accurate and comprehensive, and the presentation of the material is lucid; criticism is sound though sparing, and speculation is moderate and cautious. These qualities, and the fact that the literature on the subject is being brought up to date by the authors in Supplementary Reports, render the reviews standard sources of reference for all scientific workers in cancer research.

An interesting development of the work on pure carcinogenic hydrocarbons was the observation by Haddow, in 1935, that, in addition to their carcinogenic action at the site of injection, these hydrocarbons had a profound inhibitory effect on the growth of tumours in other parts of the body. The importance of this discovery, both from the theoretical point of view, in regard to the mechanism of carcinogenesis, and from the practical angle, with a view to possible therapeutic application, prompted an extension of these investigations to many other hydrocarbons and their derivatives. The subjects of the five communications (XXI–XXV) on this aspect of the problem in the " Selected Papers " are indicated by the titles given at the head of this review. Paper XXV contains an account of the results of 348 experiments in which 96 different compounds were tested for their action on the growth both of transplanted tumours in mice and rats and of spontaneous tumours in mice. Paper XXIII is manifestly designed as a basis for the accurate assessment of the results of Haddow's inhibition experiments, while XXIV is a review of a rather speculative character, in which the results of tumour inhibition are considered in relation to the general nature of carcinogenesis. Impairment, rather than stimulation, of growth, is stressed as the primary influence of carcinogenic action, while the irreversibility of the neoplastic state is considered as characteristic of the established tumour cell. These factors are discussed in relation to the " Somatic Mutation Theory " of cancer.

The four papers on carcinogenesis comprise an account of the effects of 9 : 10-dimethyl- and 5 : 9 : 10-trimethyl-1 : 2-benzanthracene on the mouse's skin (XIV); a comparison of the potencies of 24 compounds (XXVI); a note on the question as to whether conversion of carcinogens into photo-oxides plays a preliminary part in their biological action (XX); and a description of unsuccessful attempts to induce tumours of the gall bladder in guinea-pigs (XVII).

Paper XV describes an extension of the work of Strong on the inhibitory effect of heptaldehyde on tumour growth. Of the aldehydes, ketones, and glucosides tested by these workers, citral and heptaldehyde were found to inhibit the growth of spontaneous tumours in mice. In Paper XVI, the interesting observation is made that there appears to be no correlation between the rate of growth of a tumour (whether growing normally or artificially inhibited) and its respiration and glycolysis values measured *in vitro*.

The subjects of the remaining papers (XXVII–XXX) are indicated by their titles. The " Selected Papers " form a valuable addition to the literature on experimental cancer, and the promise of a second volume, mentioned in the Foreword, is to be welcomed.

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EPITHELIAL TUMOURS OF THE BLADDER IN DOGS INDUCED BY PURE BETA-NAPHTHYLAMINE

by G. M. Bonser, *Journal of Pathology and Bacteriology*, **55**, 1–6, January, 1943

Since Rehn (1895) first demonstrated a causal relation between occupation in the synthetic dye industry and the development of tumours of the bladder, many hundreds of such cases have been reported in the literature. Knowledge of the incidence of this occupational disease, its geographical distribution, pathology, symptomatology and treatment, is adequately summarised in recent reviews on the subject (International Labour Office, 1921; Berenblum, 1932; Ferguson *et al.*, 1934; Hueper, 1938). The ætiology has for long been controversial. The finished dyes were clearly not responsible for the tumour formation in the bladder, and of the intermediate products used in the manufacture of the dyes, the four compounds most widely used in the industry—aniline, benzidine and alpha- and beta-naphthylamine—were considered to be the most likely causes of the disease. Final proof depended, however, on experimental evidence in animals.

The earlier experiments proved unsuccessful. Subsequently, both Schär (1930) and Perlmann & Staehler (1932) claimed to have induced tumours in rabbits with naphthylamines. The accompanying photomicrographs were, however, most unconvincing, and in a more extensive series of experiments by Berenblum & Bonser (1937), these results on rabbits could not be confirmed. The position was finally clarified by Hueper and his collaborators. They found that whereas the rabbit failed to develop tumours of the bladder following prolonged administration of beta-naphthylamine (Hueper, Briggs & Wolfe, 1938) several such tumours developed in dogs (Hueper, Wiley & Wolfe, 1938).

One problem remained undecided, however. These authors used a commercial preparation of beta-naphthylamine, and it was not possible to say whether the tumours were due to the action on the body of the naphthylamine itself or of some impurities present. This has now been established by the author of the present paper, who is Research Fellow at the Department of Experimental Pathology and Cancer Research at the University of Leeds. Using pure beta-naphthylamine, she succeeded in producing both benign and malignant tumours of the epithelial lining of the urinary bladder in 3 out of 4 dogs which were fed daily with 100–150 mg. of this substance, later increased to 700 mg. daily, for periods varying from 3 years and 8 months to 5 years. Malignancy was judged by invasion of the subepithelial tissues, including the musculature. Metastases did not occur. Other parts of the urinary tract (kidney, renal pelvis, ureters or urethra) were free from tumours.

This work finally establishes the fact that beta-naphthylamine produces tumours of the epithelium of the urinary

bladder, apart from any impurities which may be present in the product used in the synthetic dye industry.

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DISCUSSION ON THE TECHNIQUE OF RADIOTHERAPY

by B. W. Windeyer, C. Wood & R. Paterson, *Proceedings of the Royal Society of Medicine*, **36**, 261–270, March 1943

Radiotherapy is playing a part of increasing importance in the treatment of cancer of the larynx and pharynx, and three papers read at a discussion on the technique of radiotherapy held by the Section of Laryngology of the *Royal Society of Medicine* are here reported.

B. W. Windeyer, Professor of Radiotherapy at the *Middlesex Hospital*, London, gave an account of the fundamental biological and general technical principles underlying the treatment of malignant neoplasms by X-rays and gamma rays. Biologically both X and gamma radiations exercise a destructive effect on tissues; but a selective damaging effect also exists whereby some malignant tissues are destroyed by a smaller dose of radiation than that required to destroy surrounding normal tissue. This special vulnerability of tissues to radiation forms the basis of radiosensitivity. Some neoplasms such as lymphosarcoma, lymphoepithelioma and basal-cell carcinoma are naturally radiosensitive; but the majority of neoplasms are not particularly so, and special variations in technique are necessary for treatment to be successful.

In applying radiotherapy to the treatment of disease three main techniques have been employed:

(i) Multiple small dose technique. This is used for inflammatory conditions but has no place in the treatment of malignant disease

(ii) Single massive dose technique. This is of value in the treatment of small superficial malignancies of the skin; it is followed by severe reactions

(iii) Fractionated technique. This is the most useful X-ray technique for the treatment of malignant disease. The time factor is an important consideration, as the treatment must be designed and given as a single course made up of fractional doses given on successive days. The total treatment time should not exceed 30–35 days, otherwise the malignant cells may become immune to the effects of the radiation.

The value of protraction of the individual treatment by the use of a low dosage rate is not yet established. Meanwhile the use of a high dosage rate (50 *r*/min.) rather than a low one (5 *r*/min.) has obvious economical advantages.

The quality of X-ray beam used in the treatment of individual lesions requires variation according to the position of the tumour in the tissues. For superficial neoplasms low voltage X-rays (60–100 kv.) are very useful. Most of the tumours of interest to the laryngologist are situated at a limited depth below the skin surface and X-rays of high voltage (180–250 kv.) are adequate. Supervoltage X-rays (250 kv. or more) are of value in the treatment of more deeply seated tumours such as carcinoma of the thoracic œsophagus.

In planning treatment for the individual case of cancer attention to detail and accuracy are important. The number, size, position and direction of the fields will depend on the situation, extent and character of the lesion and the presence or absence of metastases. For highly radiosensitive tumours with widespread metastases a few large fields may be used. Squamous cell carcinoma, however, requires multiple small field methods with accurate beam direction. The dose required for each of the various types of tumour is not yet known. Success does not depend on the actual dose delivered to the neoplasm, but the reactions of the tissues to the dose given are also of the greatest importance. Radiotherapy for malignant disease of the mouth and throat causes severe local reactions and depresses the general condition of the patient. It should not be regarded as an easy alternative to surgery.

Dr. Constance Wood, Director of the Radiotherapeutic Research Unit at the *Hammersmith Hospital*, London, dealt with the technique of teleradium treatment of cancer of the head and neck. At this centre a 10 g. radium beam unit is used, and with the aid of a special directional caliper, accurate treatment can be given through small fields. Before undertaking teleradium treatment to the head and neck regions, all septic teeth should be removed and the gums should be allowed to heal. In some cases of cancer of the larynx and pharynx a preliminary tracheotomy may be necessary, although in certain cases radiation treatment may prevent the need for this operation. Treatment should be so planned that the primary disease and its probable lines of spread should be adequately and homogeneously irradiated. As the quantity of radiation tolerated by a patient is limited, it is an advantage when treating cancer of the oral cavity or pharynx to irradiate the primary growth through its areas of lymph drainage in the neck. During treatment the general condition of the patient requires careful attention. The diet is important in these cases, since the radiation reaction of the mucous membranes of the mouth and pharynx interferes with proper feeding. The calory intake should be controlled and the diet should be high in vitamin content. From graphical records of the daily progress of dosage and the general and local responses of the patient to treatment the following observations were made:

(i) The best results were observed when the dose was approximately 6–7,000 *r* given in 42 days

(ii) Chief among the general constitutional effects were loss of weight and diminution of the total leucocytes, mainly lymphocytes, of the blood count

(iii) Locally, membranous reaction is noted at the primary site at the end of a week, reaching its maximum in the fourth week, and then subsiding. The skin reaction occurs later than the mucous membrane reaction, often not until the third or fourth week.

Dr. Ralston Paterson, Director of the *Holt Radium Institute*, Manchester, discussed the radiotherapeutic treatment of cancer of the pharynx and larynx. The two main types of malignant neoplasm affecting the larynx and pharynx are squamous cell cancer and reticulo-endothelial growths. The distinction between these two types is important as the principles of treatment differ in each case.

(1) Squamous cell cancer. This is the commonest type and where cure is intended the fundamental need of treatment is to irradiate the smallest volume of tissue which will adequately include the whole tumour, to the highest dose which will be safely tolerated. The chief methods of treatment are external radiation by X-rays or teleradium, but the following radium procedures are of value:

(*a*) Finzi-Harmer fenestration implant for growths of the middle third of the vocal cord

(*b*) Sponge rubber applicators for superficial growths of the post-nasal space

(*c*) Radon seed implantation of the oropharynx

(*d*) Combined radium collar and radium bougie for limited growths of the hypopharynx.

Radiation is of value in the palliative treatment of squamous cell cancer because it can relieve symptoms and prolong life. Such treatment should not be radical; the dosage given should be below maximum and the treatment time should be short.

(2) Reticulo-endothelial growths. This term includes such varieties as lymphosarcoma, reticulum cell sarcoma, lympho-epithelioma, endothelioma and round cell sarcoma. These tumours have two common characteristics: they are radiosensitive and radioresoluble. By radiosensitive is meant that they disappear quickly under radiation, and by

radioresoluble that there is no local recurrence in the area treated. The advantages of radioresolubility are minimised because these tumours disseminate early and widely. In contrast to squamous cancer, large volumes of tissue require radiation even when the disease appears limited. Success depends on early treatment before general dissemination has occurred, and a radical dosage whereby the whole of a large volume of tissue is treated to the limits of tolerance. Wide field X-ray therapy provides the best method of treatment for the reticulo-endothelial growths; radium is not a satisfactory alternative.

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BEAM DIRECTION IN RADIOTHERAPY: *Symposium* by F. Ellis, C. W. Wilson, J. L. Dobbie, L. G. Grimmett & T. A. Green, *British Journal of Radiology*, **16**, 31–43, February 1943

This symposium contains papers read at a recent meeting of the Radiotherapy Section of the *Faculty of Radiologists*. The expression Beam Direction is used to describe all methods which make more exact the treatment of malignant tumours by means of converging beams of X and γ rays. The problem has two aspects: first, the exact localisation of the tumour, and, secondly, the correct application of the therapeutic radiation beams under fixed geometrical conditions. The methods which have been developed may deal with the second question only, or may deal with both in combination. Although, in general, deep-seated tumours are considered, others, such as breast tumours, may also be suitable for the application of similar ideas.

F. Ellis of the *Sheffield Radium Centre* discusses the requirements of tumour localisation, and classifies methods of treatment more fully described in subsequent contributions. Methods of localisation usually depend on rendering the tumour radiographically visible. Implanted radon seeds, soft-tissue shadows, barium swallowed or injected through a catheter, and tomographs, are used in appropriate sites. Even so, the total size of the tumour is a matter calling for judicious estimation.

Beam Direction may depend on the judgment of the therapist, who makes the necessary adjustments by eye on each occasion. Alternatively, mechanical means, sometimes depending on skin marks or fluoroscopy, may be used. The author refers to an instrument which he has planned but not yet executed, and which, he hopes, will make possible treatment in any plane. This is a device for directing a beam of X-rays by means of an arc attached to the patient. The author also refers to the possibilities of rotational therapy.

C. W. Wilson of the Physics Department of *Westminster Hospital*, London, points out that in order to produce a desirable distribution of radiation in an isolated deep volume of tissues, it may be necessary to direct the several beams employed not at the centre of such a volume but at some other (usually deeper) point. Such a case is illustrated in the treatment of carcinoma of the larynx by means of 3 teleradium beams whose central axes intersect at a point 2 cm. behind the larynx, thus superimposing the area of high dosage on the area occupied by the larynx itself. To ensure the correct application of the radium bomb in these predetermined positions, a bridge-like device rising from a base-board is placed over the neck, and carries wooden discs on which the radium bomb is located.

As an example of similar principles applied to X-ray therapy, the author considers a tumour of the lung and shows that, by careful consideration of the dose-contours, two fields may be used in place of three, with improvement of depth-dose.

J. L. Dobbie of the *Holt Radium Institute*, Manchester, describes and illustrates two different systems of X-ray Beam Direction. The first method involves the construction for each patient of a rigid envelope in the form of a cap, collar, or jacket, to fit the part containing the tumour. These envelopes may be made of plaster bandage or sheet plastic material. The tumour is localised within the envelope and a suitable arrangement of treating beams is decided. The points of entry of their central axes are marked by wax seatings to locate the X-ray tube applicator, and the points of emergence are marked by small holes. During treatment a device is fixed to the X-ray tube which carries a pointer lying in the central axis of the beam. The patient wears the envelope, the applicator is located on the wax seating, and the pointer must engage in the appropriate hole on the far side of the envelope.

The second method is preferred where compression is important. The apparatus consists either of a bridge-like protractor placed across the patient, and centred on the previously determined position of the tumour, or of a portion of such a protractor attached to the X-ray tube in such a way that the applicator can be advanced towards the centre of the protractor, which is kept fixed in the predetermined position of the tumour. In both cases the direction of the beam and the tumour depth are read directly on appropriate scales.

T. A. Green of the Radiotherapy Department, *St. Thomas's Hospital*, London, had previously (1937) described a "caliper" for use with a teleradium unit, and he now describes a similar design suitable for attachment to an X-ray tube. This device is used with skin marks showing points of entrance and emergence of a line through the tumour. During treatment the applicator is applied at one skin mark while a pointer carried in the central axis on a movable arm is made to coincide with the other skin mark.

When compression is to be applied an arrangement as determined by the caliper is first made. A fixed pointer is then brought up to a scale on the applicator. As the tube is lowered to effect compression, adjustment of the couch or tube is made to keep the stationary pointer on the scale, which then shows the amount of movement in the direction of the central axis of the applicator.

In addition to movement in the central axis, the pointer of the caliper is capable of regulated movement for a considerable distance round it, so that by applying the pointer to any part of the patient's surface, the relation of that part to the dose contours of the beam can be determined. This modification finds special application in breast treatments.

When the vertical depth of a tumour below a skin mark is known, the direction and length of any path from it to points on the patient's skin can be reconstructed in space by a device which erects on any selected point a vertical line equal to the known vertical depth below the skin mark, and thus allows a parallelogram to be completed by a line equal in length and direction to the line joining the selected skin point and the tumour. The author describes a useful instrument for this purpose, which is fully illustrated in the original paper.

A second method of deriving the same information for the same purpose is provided by an arc which can be held suspended over the patient with a vertical radius centred on the tumour at known depths. Other radii, which may be provided by a ray of light from a lamp sliding round the arc, indicate skin points at known directions and distances from the tumour.

In the "predetermined shape method" the tissues to be treated, say, breast or neck, are enclosed in a close-fitting open box suitably shaped, and having two, three, or more sides. The unoccupied space within the box is filled with packing, and treatment is applied through each side in turn. In this way, fixed treating conditions are ensured, and exact dosage can be worked out.

L. G. Grimmett describes a development of the teleradium caliper designed by Green. This consists of an electrical system incorporated in the emergent pointer which rings a bell if the patient moves, beyond certain small limits, from his correct position during treatment.

The original papers of this symposium are accompanied by drawings and photographs which contribute greatly to their interest.

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THE TELERADIUM TREATMENT OF INTRINSIC CANCER OF THE LARYNX

by M. Lederman & W. A. Mill, *Journal of Laryngology and Otology*, **57**, 471–488, November 1942

There are three main radiotherapeutic methods available for treating intrinsic cancer of the larynx. These are:

(1) High voltage X-ray therapy.
(2) Fenestration of the larynx and radium implantation (Finzi-Harmer operation).
(3) Teleradium therapy (Radium "bomb" or "beam" therapy).

Of these methods, the last is probably the least commonly practised. The authors who are, respectively, Radium

Therapist and Laryngologist to the *Royal Cancer Hospital*, London, report a series of 35 cases treated at this centre by a 5 gram and 1 gram teleradium unit.

Under the term intrinsic cancer of the larynx they include neoplasms arising on the true cords, false cords, and ventricle, and the anterior and posterior commissures. Most of the cases treated showed advanced disease, only four cases being suitable for laryngo-fissure or fenestration. Ten were suitable for laryngectomy; nine, while technically operable, were unsuitable for laryngectomy because of the general condition of the patient; three cases were unsuitable for any form of surgical treatment. The authors advise biopsy in all cases with two possible contra-indications: (1) a patient with respiratory embarrassment and œdema can often be saved from a tracheotomy by correct radiotherapeutic treatment, but this may be prevented by an ill-advised biopsy, and (2) it is sometimes technically difficult tc perform direct laryngoscopy on patients with short necks and good teeth. The authors do not insist upon biopsy in such cases if the clinical diagnosis seems certain.

Teleradium treatment is planned according to the general condition of the patient and the extent of the local disease. Treatment is restricted to the larynx, and the cervical lymph node areas are treated only if metastases are suspected on clinical grounds. A small field, 3·5 to 5 cm. in diameter, is placed over each thyroid ala, and these are sometimes supplemented by a third anterior field placed over the *pomum adami*. Two fields are treated each day for 6 days per week, each field receiving 300–350 *r* per treatment. The dose given depends on the response seen in each individual case; generally an attempt is made to deliver a tumour dose of 6–7,000 *r* in 4–6 weeks.

The chief complications of radiotherapeutic treatment are:

(1) Œdema, which may be seen during or after treatment. Its significance depends on the time relationship. When observed before treatment is begun, it may be due to sepsis. It is always an important sign and has a marked influence on the course of the treatment.

(2) Necrosis of the larynx is now much less common than formerly, and can be classified as follows:

(*a*) Immediate necrosis, which shows itself soon after the completion of treatment, without an intervening stage of healing.
(*b*) Early necrosis, which occurs within six to twelve months after apparent healing.
(*c*) Late necrosis, which occurs after healing which has lasted for a year or more.

Although the time periods are arbitrary the descriptive terms are of significance. Immediate and early necroses are usually due to faulty technique or over-dosage and are avoidable. Late necrosis is due to post-radiation *endarteritis obliterans* for which there is no known means of direct prevention. There were three cases of laryngeal necrosis among the thirty-five treated in the present series. All were probably due to a fault in technique which has now been corrected, and for the last four years no case of laryngeal necrosis has been seen.

(3) The authors strongly deprecate the performance of a tracheotomy either before or during treatment, as such cases never seem to do well. This operation was found necessary after treatment in four cases. In two cases a tracheotomy had to be performed as a palliative measure because the disease was not eradicated, in the remaining two cases because of necrosis or œdema.

The following plan is recommended for the treatment of recurrences:

A. For post-operative local recurrence teleradium is indicated as a curative or palliative method, while for recurrences after radiotherapeutic treatment excisional surgery is the best method, if possible. A second radiotherapeutic treatment is dangerous and rarely successful.

B. Cervical lymph node metastases present problems in treatment which have not yet been satisfactorily solved. Where no previous treatment has been given, teleradium is advised for, both operable and inoperable lymph node metastases. If metastases occur in a region previously treated by radiotherapy surgical excision is indicated, or if this is not possible implantation of radium needles or radon seeds may be of palliative value. Lymph node recurrences after surgical removal of cervical lymph node areas can occasionally be successfully treated by teleradium. Implantation of radium or radon is often the quickest and simplest way of dealing with these cases.

There is a marked scarcity of published results of radiotherapeutic treatment of intrinsic cancer of the larynx. This can be remedied only if more cases are sent to the radiotherapist. Statistically significant results cannot be deduced from the present small series of cases, but as an index of the value of teleradium treatment the authors point out that, of 15 previously untreated cases observed for five years after treatment, 7 are known to be alive and well, one who is now untraceable was known to have had two years' freedom from symptoms, and one further patient died of intercurrent disease, *post mortem* examination of the larynx showing no evidence of cancer.

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THE VALUE OF POST-OPERATIVE RADIOTHERAPY IN CARCINOMA OF THE BREAST

by R. McWhirter, *Edinburgh Medical Journal*, **50**, 193–207, April 1943

The results obtained by radical mastectomy for early breast cancer probably represent the peak of surgical achievement in the treatment of cancer. Yet mammary cancer is the cause of approximately 20 % of cancer deaths in women; and moreover this percentage is remorselessly increasing.

The author, who is Radiologist to the *Royal Infirmary*, Edinburgh, attempts to prove that post-operative radiotherapy is of significant value in the treatment of breast cancer. It is notoriously difficult to determine and compare accurately the results obtained in the treatment of cancer of the breast by different methods. A uniform system of classification of cases according to the stage of advancement of the disease is essential for such a comparison to be satisfactory. The author uses the following scheme:

Stage I. Growth confined to the breast. Involvement of an area of skin directly over the tumour does not affect the staging. Paget's disease of the nipple is regarded as belonging to Stage I in the absence of palpable lymph nodes.

Stage II. As Stage I, but with palpable mobile lymph nodes in the axilla.

Stage III. The growth extends beyond the *corpus mammæ*, either deeply to the underlying muscle or superficially to the skin, which is invaded over a large area in relation to the size of the breast. Axillary lymph nodes if palpable must be mobile.

Stage IV. The growth has extended outside the breast area, *i.e.* fixed axillary lymph nodes, complete fixation of tumour to chest wall, supraclavicular or cutaneous metastases, or metastases in opposite breast or distant organs.

Records of 1879 cases of cancer of the breast seen between 1930–1942 were available. Of these cases 30 % were Stage I, 17 % Stage II, 20 % Stage III, and 21 % Stage IV. The remaining 12 % were not staged.

The methods of treatment selected for comparison were (*a*) radical surgery alone, and (*b*) surgery (either local or radical) associated with a full course of post-operative X-ray therapy. The radiotherapeutic treatment was considered adequate with doses of 3,500–4,500 *r* given in 3–4 weeks. The area treated comprised the chest wall and axillary and supraclavicular lymph nodes on the affected side. Only the cases forming Stages I–III were used for investigation since it was found that survival for 5 years in the Stage IV cases was negligible, no matter what the method of treatment employed.

The three-year symptom-free rate was chosen as the basis for comparison, as it was found statistically that this and the five-year survival-rate were almost equal (38 % and 37 % respectively for 566 cases in Stages I, II, and III).

The effect of post-operative radiotherapy (i) on the local recurrence rate in the operative field, and (ii) when the axillary lymph nodes are diseased were analysed in detail.

(i) It was found that post-operative radiotherapy was effective in destroying cells left behind in the "treatable area," *i.e.* the chest wall, axilla and supraclavicular regions. The recurrence rate in the treatable area was reduced by 18–20 % in all Stages when post-operative radiotherapy was employed, and the three-year symptom-free rate was increased by 22 %, 32 % and 23 % in Stages I, II and III respectively by the same means.

(ii) In order to assess the effect of post-operative radiotherapy on the axillary lymph nodes, the cases were arranged into two groups, one without histological evidence of

axillary lymph node invasion and the other where such invasion was present. The three-year symptom-free rate for radical surgery alone was 57 % when the lymph nodes were histologically negative and 24 % when the nodes were involved. The comparable figures where post-operative radiotherapy was employed were 91 % and 50 %. It would therefore seem that post-operative radiotherapy can be relied upon to destroy malignant cells left behind in the axilla, and as the complete removal of axillary lymph nodes by surgery is never an easy matter the author has considered the possibilities of treating cases by local removal of the breast, leaving the axilla untouched, coupled with a full course of post-operative radiotherapy. Even should this method prove no more effective than the radical operation plus radiotherapy it is still preferable, as the operative mortality is reduced and there is less subsequent disability. From observations extending over a year the results of simple mastectomy and radiotherapy appear to be as good as those following the radical operation and radiotherapy. A note of warning, however, is necessary as this method is still on trial and should not be adopted in centres where effective post-operative radiotherapy is not available.

The paper concludes with observations on the need for the early diagnosis and treatment of breast cancer. The average delay occurring before treatment is instituted is 9 months, and is largely due to the present outlook and organisation of medical practice. Were this delay eliminated, 50 % of cases of breast cancer could be cured by modern methods of treatment.

BIOLOGICAL EFFECTS OF X-RADIATION

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EFFECT OF X-RAYS ON AQUEOUS SOLUTIONS OF BIOLOGICALLY ACTIVE COMPOUNDS

by W. M. Dale, *British Journal of Radiology*, **16**, 171–172, June 1943

This paper outlines a series of investigations (Dale, 1940; 1942; 1943; Dale, Meredith & Tweedie, 1943) from the *Christie Hospital and Holt Radium Institute*, Manchester, on the effect of X-rays on aqueous solutions of biologically active compounds.

On exposing a wide range of concentrations of solutions of the crystalline enzyme carboxypeptidase to X-rays it was found that, for instance, a dose of 50 *r* inactivated about 30 % of a dilute solution, whereas a dose of 100,000 *r* was required to produce the same percentage effect on a solution 340 times as concentrated. A dilute solution, therefore, can be almost completely destroyed by a small dose, when a concentrated solution exposed to the same dose would appear unaffected (radioresistant). This may be briefly called the " dilution effect."

The quantitative test showed that for a given percentage destruction and a given dose of X-rays the absolute amount of the enzyme destroyed is constant whatever the initial concentration. This result can only be understood by assuming an *indirect* action of the radiation causing the formation of an intermediate product (Fricke, 1934; Hopwood, 1940; Luria & Exner, 1941; Risse, 1930; Gray & Read, 1942) from the solvent (water) which then acts on the enzyme. A direct action (" hit " theory) would require that the amount of enzyme inactivated increases with increasing concentration (the number of effective hits being proportional to the concentration).

When carboxypeptidase is irradiated in the presence of its substrate no inactivation takes place. This " protection effect " was analysed in the case of the enzyme d-amino-acid oxidase, which can be split into the prosthetic group flavine-adenine-dinucleotide and its specific protein, both of which together are necessary for enzymatic activity. Each one of these components is radiosensitive, though not equally, and if mixed, after being irradiated separately, they yield the greatest inactivation, whereas irradiation after mixing shows the " protection effect."

On adding a great variety of other substances (amino acids, sugars, nucleic acids, etc.), one at a time, to either of the two enzyme components protection again took place, proving that no specific compound of changed radiosensitivity was the cause of this protection. Sodium chloride did not protect at all. When the concentration of the substance added was progressively decreased, a corresponding decrease of the protection occurred. It was thus possible to determine for a given dose of X-rays the concentration of any of the substances added which was needed to protect to 50 %.

The indirect action concept simultaneously explains the protection phenomenon. If the intermediate product encounters two or more different solutes, and if these solutes are capable of reacting with it, each one will share in the reaction according to its concentration and affinity, leaving a larger or smaller share for its partner.

The indirect mode of action of X-rays and its consequences —the dilution and protection phenomena—can be shown to hold also for acetylcholine as a representative of an organic, non-protein, biologically active substance entirely unrelated to enzymes.

According to these investigations radiosensitivity will depend:

(*a*) on the specific affinity between the substance in question and the intermediate product formed from water during irradiation
(*b*) on the affinity of other substances present at the same time (protection effect)
(*c*) on the relative concentrations (dilution effect)
(*d*) on the particular physiological action of these substances.

With regard to the biological effects of X-rays (Evans, Slaughter, Little & Faila, 1942) on the more complex living matter, the following points may be mentioned as being in agreement with the results of these *in vitro* experiments:

(i) The unspecific though graded response of living matter to irradiation finds its counterpart in the susceptibility of so great a variety of substances responding to radiation
(ii) The great radiosensitivity of " specific " proteins which, unsurpassed by any other substance in these investigations, is in marked contrast to the gross changes of viscosity, precipitation, etc., of unspecific proteins seen after very intensive irradiation
(iii) The fact that younger cells, and especially embryonic cells, are more radiosensitive than older ones (greater general water content), and also that dry seeds are more radioresistant than seeds soaked with water
(iv) The increase of radiosensitivity of certain phases of a cell in a state of evolution in contrast to that of fully-developed long-lived cells. Here the unequal distribution of solutes enhanced by processes of mitosis and division offers the chance for the dilution and protection phenomena to come into play.

The investigations stress the importance of the indirect action theory of biological effects of radiation, in particular the radiosensitivity of enzymes if examined in suitable conditions. Earlier investigators, unaware of the protection and dilution phenomena, have used too impure and too concentrated solutions and have therefore been led to the erroneous belief that enzymes are too radioresistant to account for biological radiation effects.

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BRITISH MEDICAL BULLETIN

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The object of this Bulletin is to provide a guide to medical science and thought in Britain, and it consists mainly of summaries of a representative selection of British papers on subjects of medical interest. Any material appearing in the Bulletin may be published without fee, but acknowledgment of the source, by addition of the initial letters BMB followed by the serial numbers of the items selected, would be appreciated.

SPECIAL CONTRIBUTIONS

[This article is the first of a series of brief outlines of the development of special aspects of Medicine in Britain. The articles will be published occasionally as they are received, and the order of publication does not therefore follow a rational plan.
The object of the series is to provide, for those whose interest in medical work in Britain is of relatively recent origin, a background to the contemporary observations which are reported in British Medical Bulletin.]

THE DEVELOPMENT OF MEDICAL STUDIES IN BRITAIN: I. OPHTHALMOLOGY

by R. R. JAMES, F.R.C.S.

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Earliest Times

English ophthalmological history may be said to start with the Roman occupation of Britain. From the large number of oculists' stamps which have been unearthed on Roman sites we know that a good deal of local treatment of eye conditions by way of collyria and ointments was practised at this early date. After the withdrawal of the legions there is a long gap in our knowledge; in fact nothing is known until we come to the Anglo-Saxon *Leech* [medical] books and Herbals. Here again, treatment was mainly by local applications of infusions of herbs and the secretions of animals, such as gall mixed with honey, and even of human urine. Charms also played a large part and we may say that Anglo-Saxon ophthalmology has every appearance of having been largely futile.

The Norman Conquest and After

The Norman Conquest did little to improve the practice of ophthalmology but the 13th century saw the beginnings of optics in Britain. Grosseteste, Bishop of Lincoln, was the teacher of Roger Bacon (died 1294), who proved that spherical *plus* spheres would be of use for reading in old people; while John of Peckham (died 1294), later Archbishop of Canterbury, is credited with the discovery of the use of concave refracting surfaces, and his *Perspectiva Communis* was for the next few centuries the only text-book on optics to be used in England.

In the year 1377 John of Arderne wrote his little book entitled *De cura oculorum*, of which manuscripts in Latin and in 15th-century English exist among the *Sloane Manuscripts* at the British Museum, and in the Library of Emmanuel College, Cambridge. This booklet is a mere compilation of other people's views, much of it being taken from Lanfranc. English ophthalmology had, in fact, made very little progress since Anglo-Saxon times.

The Sixteenth and Seventeenth Centuries

The closing years of the 16th century saw the publication of two small books dealing with ophthalmology. One was Walter Bayley's *Briefe Treatise Touching the Preservation of the Eye-sighte*, and the other a translation (probably by A. Hunton, of Newark-on-Trent) of Guillemeau's *Maladies de l'Œil.*

Early in the 17th century Richard Banister, of Stamford, brought out a duodecimo of 478 pages containing five separate treatises. Of these the first 112 pages are Banister's own contribution, and this section is named Banister's Breviary. Though he was an itinerant oculist it is obvious that Banister was a much more honest practitioner than the rest of his ophthalmic contemporaries. He it was who first pointed out the cardinal sign of hardness of the eyeball in cases of *gutta serena*, in this case glaucoma. The significance of his observation was not recognised, and raised intra-ocular tension was forgotten for the next 150 years. Banister was also almost certainly the author of the manuscript in the British Museum (*Sloane Manuscript*, 3801) which throws much light on the manners and customs of the itinerant charlatans of this date. Several of these are named, such as Luke of Erith, Mr. Surphlete of King's Lynn, and Henry Blackborne. The last-named is severely criticised by Banister, and it is a sign of the looseness of the times that Blackborne in 1605 received the Archbishop of Canterbury's licence to practise in diseases of the eyes. Richard Banister must have been a remarkable man and has deserved well of ophthalmology.

Turberville of Salisbury (died 1696) was a qualified medical man in an age of unqualified quacks. He had a large practice and made a valuable contribution to ophthalmology in extracting an iron particle from the cornea with a magnet. Another qualified English physician of this time was William Briggs, who published the *Ophthalmographia* and the *Nova Visionis Theoria.* He described the papilla of the optic nerve in 1676 and, in 1684, recorded in the *Philosophical Transactions of the Royal Society* a case of night-blindness. Dimness of vision following the administration of Peruvian bark in fever was described in 1681 by a general practitioner at King's Lynn in a letter to Briggs.

The Eighteenth Century: Charlatinism and the Foundations of Modern Ophthalmology

The 18th century was the age of ophthalmic quackery, but it saw the foundations of modern ophthalmology laid by such masters as Cheselden, Sharp and Warner. Cheselden devised the operation of iridotomy in the making of an artificial pupil, and Sharp and Warner perfected the operation of extraction of cataract, a great advance on the age-long method of couching [displacement of the cataract from the visual axis].

Duddell, a pupil of Woolhouse, wrote a good account of diseases of the cornea in 1729. Later in the century, James Ware wrote on syphilis in connexion with ophthalmia, and brought some order out of chaos in the matter of conjunctival diseases. Gataker wrote on the anatomy of the eye and on the use of belladonna, and Wells on double vision.

The chief 18th-century ophthalmic quacks were William Read, Roger Grant, and the Chevalier Taylor. Read and Grant were illiterate; the former was knighted by Queen Anne. The Chevalier Taylor was quite a remarkable person. In professional knowledge he was often far ahead of his time, but he practised all the arts of unblushing effrontery and charlatanism. He was oculist to George II, and his son and grandson followed in his footsteps though they were not of the same calibre. Eighteenth-century Royalty was singularly unfortunate in its oculists, as George Coats pointed out.

The end of the century, in 1794, saw the publication by John Dalton of the history of his colour blindness. Thus, it will be seen that up to the end of the 18th century ophthalmology had not advanced very far, but better times were to come.

Rational Ophthalmology Displaces Charlatanism

The year 1805 saw the foundation of **Moorfields* Eye Hospital by J. C. Saunders, and this more than anything else struck the death blow to the quackery of the previous century. Provincial Eye Hospitals were founded at Exeter in 1808, Bristol in 1810, and Manchester in 1814. The *Royal Westminster* Ophthalmic Hospital was founded by Guthrie in 1816, the *Central London* Ophthalmic Hospital in 1843, the *Western* Ophthalmic Hospital in 1856 and the *Royal* Eye Hospital in the year following. The first course of lectures on diseases of the eye was given by Guthrie at the *Royal Westminster* Ophthalmic Hospital.

An earlier epoch-making date in ophthalmological history is 1801, when Thomas Young published his paper on the mechanism of the human eye in the *Philosophical Transactions.* He described astigmatism and measured the amount of the astigmatism in his own eye. His table of optical constants has been only very slightly modified by modern research. His theory of colour vision postulated the presence in the

* [Now the *Royal London* Ophthalmic Hospital.]

retina of three "fibres," which correspond to the colours red, green and violet respectively. This theory was later resuscitated by Helmholtz and is known as the Young-Helmholtz theory. Young's experiments on interference strongly supported the undulatory theory of light already adumbrated by Sir Isaac Newton and Huygens.

Ophthalmological Literature and Societies

The first real text-books of ophthalmology in Britain belong to the first half of this century. In 1830 William Mackenzie of Glasgow brought out his great work on diseases of the eye. It was far ahead of any previous text-book on the subject and it ran to a fourth edition. Mackenzie was a master clinician, and was the first surgeon to give an adequate account of sympathetic ophthalmitis. Sir William Lawrence's text-book appeared in 1833, and Richard Middlemore's in 1835. Before this, Travers had brought out his synopsis of diseases of the eye in 1820. It ran to a third edition. J. C. Saunders published a book before his untimely death, and did much to revolutionize the treatment of congenital cataract by insisting on early discission. In this he followed the practice of Woolhouse, an English surgeon, who was resident in Paris for many years in the previous century.

Wardrop's *Essay on the Morbid Anatomy of the Human Eye* laid the foundations of ophthalmic pathology; Tyrrell's *Diseases of the Eye*, in two volumes, appeared in 1840; and Dalrymple's splendid atlas belongs to about this date.

The year 1881 saw the foundation of the *Ophthalmological Society of the United Kingdom* with Sir William Bowman as first president. It grew out of informal discussions in the house-surgeon's room at old *Moorfields*, and of the Committee appointed to make arrangements for its foundation Sir Thomas Barlow is the sole survivor. Sir H. Lindo Ferguson of New Zealand is also still with us as an original member of the Society. The Society now has, as affiliated members, the *Oxford Congress*, founded by R. W. Doyne, the *North of England Ophthalmological Society*, founded by Percival Hay and J. Gray Clegg, the *Midland and South Western* Societies, the *Irish Ophthalmological Society*, and the *Scottish Ophthalmic Club*. A volume of *Transactions* has been published each year without a break since 1881, and the series forms a rich mine of ophthalmological facts.

In 1857 the staff at *Moorfields* began the publication of the invaluable *Ophthalmic Hospital Reports*, which ran to 20 volumes. In 1864 J. Z. Laurence and T. Windsor began the publication of the old *Ophthalmic Review*. It came to an untimely end 3½ years later and the new *Review* was started in 1881 by Priestley Smith of Birmingham and Karl Grossmann of Manchester. The *Ophthalmoscope* was founded by Sydney Stephenson in 1903. In 1917 the first number of the *British Journal of Ophthalmology* appeared. It incorporates the *Moorfields' Reports*, the *Ophthalmic Review* and the *Ophthalmoscope*, and has continued without a break to the present day.

Ophthalmic Instruments and Operations

English ophthalmology has been responsible for many inventions of ophthalmic instruments. It should not be forgotten that William Porterfield (died 1771) devised the first optometer. Charles Babbage, in 1848 constructed an opthalmoscope which left little to be desired. He showed it to Wharton Jones, who, alas! did not realize the importance of the means of research thus placed at his disposal. Babbage was a mathematician, not an ophthalmic surgeon, and finding that Wharton Jones was not interested in his model he took no further steps and it was left to Helmholtz to bring out his instrument in 1851. Tyrrell devised the iris hook which bears his name; Bowman a trephine for the eye-ball; Mules of Manchester first suggested the insertion of a glass globe in the sclerotic after evisceration of the eyeball, and his practice was later modified by Frost and Lang, who inserted globes of glass or metal into the orbit.

Corneo-sclerotic trephining for chronic glaucoma was first proposed by Freeland Fergus of Glasgow in 1909. In the next year Elliot, of Madras, improved the operation by splitting the superficial layers of the cornea in order to make more sure of tapping the anterior chamber, and the operation has been known by his name ever since. Herbert, of the Indian Medical Service, also made important additions to our anti-glaucoma methods at this date.

Stanford Morton's ophthalmoscope was for years the best of its kind, though Frost's instrument was a close second. Frost also brought out an extremely effective model eye for teaching purposes.

Ophthalmology as a Speciality

In the early years of the last century ophthalmology was still, in Britain, a part of General Surgery; Sir William Bowman was the first general surgeon to give up his surgical work at *King's College* Hospital in order to become a pure ophthalmic specialist. With George Critchett, Bowman was responsible for the foundation of this speciality. But Critchett, and even Jonathan Hutchinson, were general surgeons primarily and ophthalmic surgeons in the second place.

Bowman's name is a household word in ophthalmology. Bowman's membrane, his probes, and "stop" needles are known everywhere; but it was his guiding hand which placed ophthalmology as a speciality on a sure footing. Lawrence wrote on syphilis of the eye. Hutchinson's monograph on syphilitic disease of the eye and ear is a classic, and he was the first to describe the notched incisors in congenital syphilis which will always be known as "Hutchinson's teeth." It is reputed that a French surgeon who visited Moorfields in the early 60's rushed into the out-patient room exclaiming "Where is Monsieur Hutchinson? I want to see his teeth."

Hutchinson's main assistants were Waren Tay and Edward Nettleship. Tay never cared for publicity and was glad to remain in the background. Hutchinson's mantle may be said to have fallen on Nettleship, who had a profound influence in the teaching of ophthalmology in his generation.

Argyll Robertson first described the tabetic pupillary reactions which have ever since borne his name; and in an earlier decade Arthur Jacob, of Dublin, first described the layer of rods and cones in the retina in 1819.

One of the first atlases of the fundus was that of Liebreich who was ophthalmic surgeon to *St. Thomas's* Hospital. He had been turned out of Paris at the beginning of the Franco-Prussian War of 1870, and came to England. There have been several good atlases since his day, notably that of Frost, the pictures in which are still unsurpassed.

Ophthalmic pathology has been well served by the long line of curators of the museum at *Moorfields* Hospital. Nettleship, Lawford, Treacher Collins, all made notable contributions in this subject, but George Coats, who died in 1915, probably contributed more papers of lasting value than any other, with the exception of Sir John Parsons whose magnificent *Pathology of the Eye* in four volumes has long been a credit to British ophthalmology.

For many years the importance of the state of the refraction of the eye was overlooked and underestimated. A case of Brudenell Carter's, published in the Clinical Society's *Transactions*, in 1875, was one of the first to call attention to the importance of this branch of work; and partly in consequence a demand arose for hand-books on refraction; among these, that of Hartridge ran through many editions and was deservedly popular.

In the field of medical ophthalmology, the manual by Sir William Gowers was pre-eminent for many years: its third edition was brought out by Marcus Gunn who, from his experience as Ophthalmic Surgeon to the *National* Hospital, Queen Square, did much to advance ophthalmology in its relations to neurology. Perimeters have been invented by McHardy, by Priestley Smith and by Sir William Lister. Priestley Smith won the Jacksonian prize at the *Royal College of Surgeons* in 1878 with his essay on glaucoma. Few men have had more influence on their speciality of recent years than this celebrated Birmingham ophthalmologist.

Ophthalmological Education

Postgraduate education in ophthalmology is given at the universities and at all the great eye hospitals in London and the provinces. Courses of lectures which include all ancillary subjects such as optics, operative surgery, bacteriology and pathology are given during the terms, and at the same time the student takes his place as clinical assistant to one or more of the members of the senior staff in the out-patient department. If time is no objection, he is wise to hold the post of House Surgeon for a year or more at one of the Eye Hospitals. Even if he does not, he obtains a thorough grounding in clinical ophthalmology, and it is this aspect of teaching which has produced so many of the great names of British ophthalmology during the past hundred years. Special diplomas notably the D.O. Oxon. (1907) and the D.O.M.S. (1920) are awarded to students who pass the qualifying examinations.

and for many years ophthalmology has been one of a number of special subjects which can be taken in the examination of F.R.C.S. (Edinburgh).

Preventive and Social Aspects of Ophthalmology

Steady progress has been made during the present century both in prevention of blindness and in amelioration of the conditions of the blind. Blind pensions are now awarded, and ophthalmic monetary benefits under the National Health Insurance came into force in 1925.

Early in its history the *Ophthalmological Society* appointed a deputation, led by Bowman and Hutchinson, to interview the Home Secretary and draw attention to the ravages caused by *ophthalmia neonatorum*. It was pointed out that this affection is largely preventable, and it was suggested that the Registrar of Births should hand each person registering a birth a printed paper telling him what to do if the baby's eyes showed any signs of inflammation. No action was taken and little was done by the authorities until the *Metropolitan Asylums Board* established *St. Margaret's* Hospital in 1918 for the treatment of *ophthalmia neonatorum*, affording facilities for the admission to hospital of both mother and child. The *Board* also did good pioneer work by establishing, in 1903, residential schools for the treatment of trachoma in children, at the same time ensuring the continuance of their education.

The *London County Council*, at the instigation of Mr. James Kerr and Mr. Bishop Harman, made a notable advance by segregating partially-sighted children in special—so-called "myope"—schools. Valuable reports on the prevention of blindness have emanated from Glasgow in 1926 and in 1942, and from the Union of Counties Association for the Blind in 1932; and the Ministry of Health has at last set up a Standing Committee on the Prevention of Blindness.

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SPECIAL CONTRIBUTION

THE TASK OF OPHTHALMOLOGICAL RESEARCH

by ARNOLD SORSBY, M.D., F.R.C.S.

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I. Blindness: The Extent of the Problem

The Census returns in Great Britain, like those of most countries, used to show the number of blind persons (as also the number of those afflicted with certain other physical disabilities). These returns, based on information supplied by the persons affected, or by relatives on their behalf, had the limitations inherent in any lay assessment of a technical problem, and the number of 26,366 persons returned as blind in the 1911 Census of England and Wales must therefore be taken with some reserve. With the Blind Persons Act of 1920, the practice of seeking to assess the number of blind by Census enquiries was discontinued as it was believed that the Register of those who would seek the statutory benefits (blind pensions, training facilities, etc.) which the Act allowed would be a more complete representation of the position, particularly as only those certified blind by a medical examiner would be registered.

The first year of registration (1919) showed the number of blind as 25,840, a close approximation to the Census figure, but this number has increased steadily year by year. It was 30,785 in 1920, 34,894 in 1921 and reached over 80,000 in 1942. It is likely that even now not all the blind are registered and that a figure of about 100,000 blind for the population of about forty million of England and Wales is not an underestimate. This gives a rate of blindness of 2·5 per 1,000, the criterion of blindness being "so blind as to be unable to perform any work for which eye-sight is essential."

On the basis of Census returns of various countries it was estimated in 1910 that there were about 3,000,000 totally blind throughout the world, but double that number has been suggested as nearer the truth. If the rate obtained for England and Wales is taken as an index for the world population, 5,000,000 would represent the blind throughout the world. But this figure is an obvious under-estimate, as the rate for blindness in countries like India and China, and throughout the Middle East, is known to be very much higher than that of England and Wales. China alone has probably about four to five million blind, and the number in India cannot be much less. Although nothing approaching an accurate estimate is possible, it is likely that there are, throughout the world, about 15,000,000 blind and many more millions with grossly defective sight.

As distinct from the immediate exciting causes of disease the great determining factors of blindness are ignorance arising from low cultural levels in communities and lack of facilities due to poorly developed medical and social services. It is therefore natural that the incidence of blindness should vary enormously in different countries as these factors are extremely variable. Within a homogeneous community economic status is a powerful determinant, as is well shown by an official health survey undertaken by the United States Government in 1936 and covering 2,498,180 persons. It was found that the incidence of blindness amongst the coloured population (mainly negroes) was 146 per 100,000 against 76 for the white population. About 18 % of the surveyed population fell into the "Relief" group, having had to seek relief from public funds at some time during the twelve months preceding the investigation, and the incidence of blindness in this group was distinctly higher than amongst the non-relief group, which in turn gave a differential rate with different income levels per family, as is seen from the following summary table:

	Rate per 100,000	*Ratio to rate in families with income of* $3,000 *and over*
All incomes	83	
Relief	163	668
Non-relief:		
Under $1,000	110	492
$1,000–1,500	59	238
$1,500–2,000	53	192
$2,000–3,000	41	135
$3,000–5,000	27	100
$5,000 and over	33	

II. The Prevention of Blindness

(i) *Infective Processes*

Whether ophthalmology has shared in the general advance towards the control and eradication of infection as a factor in disease is a debatable and not altogether academic point. It is true that prevention has all but abolished *ophthalmia neonatorum* as a cause of gross visual defect and blindness, and that affections like small-pox are no longer a significant cause of eye disease. Nevertheless, the outstanding ocular infections—trachoma and the acute ophthalmias of tropical countries—are not under control. In the case of trachoma —which affects probably about 15 % of the world's population—the exciting cause is not known with any certainty, and the acute ophthalmias of tropical countries, with their devastating lesions, are a reflection of immensely difficult problems of general sanitation and standards of living. In more developed countries, tuberculous sensitization is responsible for phlyctenular ophthalmia, the prevalent ophthal-

mia of childhood, and here the control of tuberculosis has given gratifying results in the steady decline in the incidence of the affection. Ophthalmology has undoubtedly benefited from the advances in public health and hygiene; it has also helped to limit the local infectious diseases of the eye, but it has done so more by the application of general health measures than by the specific eradication of infectious lesions.

The acute ophthalmias, tuberculous and syphilitic lesions of the eye, and trachoma exemplify the problems of ocular infectious disease. The acute ophthalmias, which are caused by a variety of organisms such as the Koch-Weeks bacillus (*Haemophilus influenzae*), the Morax-Axenfeld bacillus and the gonococcus, rank before trachoma as a cause of blindness in tropical and sub-tropical countries; the causative organisms are known, though our knowledge of the spread of these organisms is still fragmentary. It is clear that lack of cleanliness, congestion and poor sanitary conditions favour the spread of such infections, but the role of climatic, meteorological and possibly ecological factors has still to be assessed. Complex problems of individual immunity also await solution, but it is gratifying that in the meantime the sulphonamides are giving excellent results in what is still a terrible affection.

As in the acute ophthalmias, there is no mystery as to the exciting cause in tuberculous and syphilitic eye disease, but the problem here—in view of the rarity of primary ocular tuberculosis and syphilis—is how to overcome the local effect of a widespread endogenous infection. In tuberculosis and tuberculous allergy of the eye the absence of any specific treatment for tuberculosis makes the ophthalmic condition part of the general problem. In ocular syphilis a special problem is involved as the blood-eye barrier renders specific anti-syphilitic treatment largely ineffective. An anti-syphilitic agent that would reach and act on the brain and eye would be of immense value, for syphilis is responsible for about 20% of all blindness in the more advanced countries.

The difficulties of virus disease are well exemplified by trachoma. Isolation and culture of the infecting agent and the development of a specific therapy, are all as yet unsolved problems. The value of the sulphonamides in trachoma, though these are far from constituting a specific therapy, makes it possible to hope that, as in other affections, an effective remedy may be at hand even if the actual discovery of the mechanism of the disease has yet to come.

(ii) *Genetic Affections*

As infection diminishes in significance as a factor in ocular pathology, genetic disturbances assume an increasingly important position. Before the introduction (1881–84) of the Credé method [local cleansing and instillation of 1–2% silver nitrate] *ophthalmia neonatorum* was responsible for about 40% of blindness in blind schools. Now some 50% of blind children are blind from malformations and hereditary anomalies, as is seen from such studies as those conducted by Berens, Kerby & McKay (1935), and other observers. At present the possible lines on which promising work can be done are still obscure, but the emergent tendency not to make a rigid distinction between genetic and environmental factors is hopeful. Genetic disease is no longer regarded as a fixed entity. It is known that environmental factors can excite or mask an inherent genetic tendency. The control of a genetic affection such as acholuric jaundice by splenectomy, or of Niemann-Pick disease by controlled fat intake, points to the possibility of repeating clinically what can be achieved in the laboratory. The basis for *retinitis pigmentosa* and other abiotrophies is undoubtedly chromosomal, but the mechanism whereby they become manifest may well be somatic.

The limitations and possibilities of genetic research are well shown by *glioma retinae*. The recognition that this is a dominant hereditary disease in some families, places in question the status of the more common (though still rare) sporadic forms. The fact that the mode of inheritance is an irregular dominant, focuses attention on the unaffected transmitters of the disease. What are the genetic or environmental factors that lead to the suppression of the genetic potentiality towards glioma in such individuals?

(iii) *Nutritional and Metabolic disorders*

Nutritional disturbances leading to severe ocular lesions are exemplified in an extreme form by xerophthalmia, which occurs sporadically in Europe but is a major problem in countries like China, India and others of the same economic level. Less severe manifestations are a variety of ill-defined lesions due to various dietetic deficiencies. The correlation of nutrition with ocular health is still largely an unexplored chapter.

Equally obscure are the lesions of faulty general and local metabolism. Characteristic of this obscurity is the fact that the basis of diabetic retinitis is still undetermined. One difficulty underlying such investigations is the absence of any method of studying the pathological physiology of the eye. It is unlikely that an understanding of diabetic retinitis will be reached from the study of the fixed retina under the microscope, or from the biochemical analysis of the blood. Suitable methods for investigating the respiration and total metabolic activity of the intact eye will no doubt be evolved.

(iv) *Cataract and Glaucoma*

Both English and North American statistics on blindness show cataract and glaucoma to be responsible for 25–40% of all blindness. Even in countries ravaged by the acute ophthalmias and trachoma, they are formidable factors, and are naturally more significant in the higher age-groups. It is fortunate that the treatment of these two affections is in advance of knowledge of their pathology, but a fuller knowledge is essential if much blindness, and still more gross visual defects, are to be avoided. The problem here, as in the metabolic disorders, is the evolving of methods of study of the normal and pathological physiology of the eye. Analyses of opaque lenses, valuable as such procedures are, do not give much information on the processes that lead to opacification, and an exclusive physical or chemical approach to glaucoma is an over-simplification of a complex dynamic process.

(v) *Injuries*

Injuries rank high as a cause of the loss of one eye, especially in children and young adults, and are a considerable factor in the incidence of total blindness. In available English statistics, they are not so significant as in American statistics, where an incidence of 15% is often reached. Although blindness from casual injury has tended to decline in importance owing to more adequate treatment and the realization of the significance of sympathetic ophthalmia, blindness from injury as a whole tends to increase for a number of reasons. Traffic accidents in power transport, the expansion of heavy industries and of the chemical industry—to say nothing of the liberal use of high explosives in total war—all contribute to this increase. The wars of the past 70 years have been marked by an ever-increasing rate of eye injuries in relation to the total of wounds, and the present war has brought the difficult problem of extracting non-magnetic fragments from the interior of the eye, as present-day missiles are largely non-magnetic in contrast to the missiles used in the 1914–18 war. Whilst the abolition of war injuries presents a formidable political and social problem the prevention of industrial eye injuries is a tangible possibility.

War is the greatest single cause of blindness, as Kay Sharp, the Chairman of the Prevention of Blindness Committee, has pointed out. As an aftermath of the present struggle there will inevitably be starving populations, disorganised health and medical services, and possibly widespread epidemics carried by moving populations. All these are powerful determinants of eye disease, and ophthalmology will have to evolve not only services for succour, but research facilities to study a whole set of new conditions.

III. Ocular Hygiene

A hundred years ago "asthenopia" was regarded as the first stage of "amaurosis." The clear appreciation of the refraction and accommodation of the eye made possible by the work of Donders (1863) has led to an immense increase in comfort in the large sections of the population suffering from refractive anomalies—a matter of considerable importance in an industrial and educational age. It is difficult for a generation which takes optical aids as a matter of course to realize what a great handicap the absence of such aids constituted to their predecessors. So great is their value that the conditions under which the patient works have tended to be ignored. It is good that the investigation of refractive errors and muscle anomalies is constantly undergoing additional refinements, the latest example being the studies of Ames and his collaborators on optical imagery. But the need for detailed studies of conditions under which work is being done is equally great. To study the patient (or his eyes) only

and to ignore his environment is a one-sided approach. A great deal of industrial injury and disease could have been avoided by an earlier appreciation of this truism. Towards the end of the last century much attention was given to the question of satisfactory working conditions for children in a misdirected effort to prevent the development of myopia, but this has been of great value in laying the basis, not indeed for the prevention of myopia, but for the evolution of the concept of ocular hygiene. Intensive studies on environmental conditions—such as lighting and rest pauses—are needed to supplement the studies in ocular physiology.

IV. The Organisation of Ophthalmology

The rapid expansion of ophthalmic facilities in most countries has tended to be practical rather than academic. There was so much to be done in applying the great discoveries of the nineteenth century to daily life, that the more academic aspects have suffered. Nevertheless the future of ophthalmology, as of all clinical studies, depends on constant invigoration from new investigations dealing with the changed conditions and expanding the older knowledge. Ophthalmological research as a career is an essential need in the reorganisation of ophthalmic practice that is proceeding to-day. In England there is the prospect of creating a well-organised national eye service which will bring the benefit of specialised knowledge, under satisfactory conditions, to the whole population. In such a re-organised service, ample provision should be made for ophthalmic research institutes, where problems can be studied away from the pressure of the clinic, and where ophthalmic needs can be visualized from a better vantage point than the crowded out-patients' department.

The author of this article is the first holder of the Research Professorship in Ophthalmology which was established in 1943 *jointly by the Royal College of Surgeons and the Royal Eye Hospital, London.*

The growing recognition in Britain of the need for ophthalmological research has also been reflected by the formation of the University of Oxford Ophthalmological Research Endowment Committee, which has recently sponsored an appeal for funds for the endowment of a Department of Ophthalmology at Oxford for research, teaching and treatment.

Professor Sorsby, who holds the posts of Surgeon and Director of the Research Unit at the Royal Eye Hospital, was formerly the Dean of its Medical School. He is also Consulting Ophthalmologist to the London County Council, co-editor with Mr. F. Ridley of "Modern Trends in Ophthalmology" (1940), *and author of "A Short History of Ophthalmology"* (1933) *and a more general work "Medicine and Mankind"* (1941).

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A STATISTICAL ANALYSIS OF 3,219 PERSONS CERTIFIED BLIND AT THE REGIONAL CLINIC FOR CERTIFICATION OF THE BLIND, GLASGOW AND SOUTH-WEST SCOTLAND, DURING THE PERIOD 1929–1935

by J. Marshall & H. E. Seiler, *British Journal of Ophthalmology*, **26**, 327–380, 385–414 & 433–466, August, September & October 1942

In 1929 a clinic was set up in Glasgow for applicants for certification as blind persons eligible for certain statutory benefits. This clinic dealing with people from Glasgow and South-West Scotland ensured a uniform method of certification, and it was found that 3,216 (62·6%) out of 5,140 applicants during the period 1929–35 were blind within the meaning of the Blind Persons Act (" so blind as to be unable to perform any work for which eyesight is essential "). A detailed analysis of the findings in these 3,216 persons is given in the present paper and may be taken as representative of the causal factors of blindness in Great Britain, particularly as great care was taken both in the examination of applicants and in the statistical evaluation of the findings.

The three outstanding causes of blindness were cataract, myopia and venereal disease, with an incidence of 16·8%, 16·3% and 13·95% respectively. Chronic infective states (chronic septicæmia, autointoxication, *etc.*) accounted for 10·7%, and glaucoma for 8·7%. The incidence for congenital (developmental) anomalies and heredo-degenerative lesions was 7·45 %, whilst injury as a cause of blindness came surprisingly low with 6·4%, though it rose to 10·1% if the cause of blindness of one eye only was considered in patients with bilateral blindness due to two different causes.

Calculations based on the duration in years of loss of sight for each cause of blindness and the number of cases, showed that some of the major causes of blindness were not responsible for the same amount of disablement as that produced by other numerically less frequent causes. Cataract, for instance, fell from the first place to the eighth on the basis of this computation, whilst injury rose from the eighth place to the third, and congenital anomalies from the seventh to the second. On this basis chronic septicæmia took the first place with 12·0%, myopia came fourth with 10·3% and ophthalmia neonatorum fifth with 10·1%. Congenital syphilis was responsible for 7·1% and acquired syphilis for 3·8%.

The age distribution of the different causes of blindness revealed the following points of interest. In the first four years of life ophthalmia neonatorum and congenital anomalies were responsible in 68% of cases of blindness. In the school period (5–15 years) congenital syphilis and non-industrial eye injury were the major causes. In the age-group 16–29 years, syphilis was the most important single cause, but other important causes were injuries (17·3%), chronic septicæmia (16·3%) and myopia (13·3%). In the age-group 30–49 years syphilis, chiefly acquired syphilis, was responsible for one-fifth of the cases, with myopia next in importance with 17·9%. In the period 50–59 years inflammatory conditions gave way to degenerative lesions: myopia and cataract were responsible for 22·7% and 22·1% respectively. In the age-group over 70 years, cataract and glaucoma were the cause of 67% of blindness.

As to sex distribution, diabetes as a cause of blindness showed a significant excess in women, whilst men showed a considerably higher incidence of blindness due to heredo-degenerative lesions, glaucoma, acquired syphilis, injury, sympathetic ophthalmia and vascular lesions.

Amongst other points discussed in this exhaustive study are occupation as a factor in the development of blindness and the different types of complications seen in myopia at different age-periods.

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ON SOME ANOMALOUS FORMS OF AMAUROTIC IDIOCY AND THEIR BEARING ON THE RELATIONSHIP OF THE VARIOUS TYPES

by R. Wyburn-Mason, *British Journal of Ophthalmology*, **27**, *145–173 & 193–207, April & May 1943*

Since the clinical description by Tay in 1881 and the pathological account by Sachs in 1887 of the affection now known as Tay-Sachs disease, a whole series of somewhat similar clinical manifestations have been recorded. The unifying features of these affections are predilection for cerebrum and retina, the broadly similar histological features, and the relentless clinical course. The designation cerebro-macular disease, with such qualifying terms as infantile, juvenile, late infantile, late juvenile and adult types, crystallizes this unifying view. None the less there are valid reasons for doubting the accuracy of this teaching. Clinically each of these different " subdivisions " of " cerebro-macular disease " is so clearly distinct, and the genetic behaviour so markedly different, that it is difficult to visualize these different features as one. Moreover, the histological resemblances are by no means so definite as earlier observers believed; the chemical composition of the degenerate nervous tissue is distinctly different in these different affections; and it is also of considerable significance that there is no substantial

evidence of the occurrence of the different manifestations of this alleged unitary affection within the same family.

A useful contribution to this complex problem is made by the author of the present paper. In addition to reporting a number of fairly "typical" examples of the different forms of cerebro-macular disease, he describes the case of a girl aged 9 years and 9 months, suffering from indefinite neurological symptoms and showing the "cherry-red spot" characteristic of Tay-Sachs disease. This well-authenticated observation raises the question as to the validity of regarding the "cherry-red spot" as pathognomonic of the infantile form of cerebro-macular disease. In this case there was some indefinite evidence of some generalised anomaly of the lipoid metabolism, and this finding only accentuates the problem raised by previous writers as to whether Tay-Sachs disease is itself at least two distinct entities: one being a neurological degeneration and the other a generalised lipoid disturbance—the Niemann Pick disease—with fatty infiltration of the cerebrum and retinæ. It is unlikely that the prevailing confusion will find an easy solution, but observations like the one under discussion help in the elucidation of a distinctly obscure chapter in neurology and metabolic disorders.

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THE ÆTIOLOGY OF PHLYCTENULAR OPHTHALMIA

by A. Sorsby, *British Journal of Ophthalmology*, **26**, 159–179 & 189–215, April & May 1942

In Great Britain, as elsewhere in Europe and in the United States, phlyctenular ophthalmia is much less frequent than it used to be. The decline in incidence has continued steadily throughout the present century except for the years of the 1914–18 war and its aftermath. Towards the end of the last century many different bacteria had been incriminated as the cause of the affection, but evidence that the condition is somehow associated with tuberculosis emerged at the beginning of this century, when many observers found a high incidence of positive tuberculin reactions in children affected with phlyctenular ophthalmia. This evidence was strengthened by the fact that the ophthalmo-reaction to tuberculin, used as an alternative to the skin reaction, did in itself produce phlyctenular ophthalmia in some children. Further support for the tuberculous nature of the affection came with the introduction of chest radiography, when it was found that a high percentage of affected children showed some evidence of tuberculosis of the lungs.

Nevertheless, the tuberculous nature of phlyctenular ophthalmia could not be accepted as validly established, and this was for two reasons. In the first place the tubercle bacillus could not be found in the phlycten, and secondly the affection was but rarely associated with manifestations of clinical tuberculosis; phlyctenulæ were not often seen in frank cases of pulmonary or abdominal tuberculosis, nor could such generalised lesions frequently be found in children suffering from phlyctenular ophthalmia. How these contradictory data have come to be harmonised is shown in the present exhaustive study on the ætiology of phlyctenular ophthalmia. The author has had the advantage of studying the problem in a country (England) where tuberculosis is not common, and his findings are therefore free from the possible fallacy that any evidence of tuberculosis he observed in his cases is coincidental. Using the unique material available at *White Oak* Hospital, near London, where special facilities exist for children with phlyctenular ophthalmia and other chronic eye affections, the author found positive tuberculin reactions in 84·8% of 592 children under 16 years old suffering from phlyctenular ophthalmia against 15·3% in a control group of 900 cases of blepharitis. Radiological evidence of tuberculosis was present in 72·2% in the phlycten cases and in not more than 16·1% in the controls. Evidence of clinical tuberculosis was found in 6·4% of the phlycten cases, against not a single case in the control series. A family history of tuberculosis was present in 28·9% of the phlycten cases against a computed incidence of 3·7% for the normal school child population of London.

Of particular interest was the after-history of 754 phlycten cases treated at the hospital during 1921–31; 5·3% of these showed a subsequent incidence of clinical tuberculosis, and a tuberculosis mortality rate of 0·8%, in contrast to a morbidity rate of 0·8% and a mortality rate of 0·1% for 1,024 controls. Of significance, too, are the author's negative findings. Tubercle bacilli could not be recovered from gastric lavage of 50 cases, nor in the excised tonsils of 20 others. Tests for bacterial allergy, other than tubercular, were negative, and there was no evidence that malnutrition, focal sepsis or pediculosis are seen more frequently in phlyctenular ophthalmia than in control cases of blepharitis.

The author concludes that the evidence shows tuberculous infection, rather than tuberculous disease, to be the underlying factor in phlyctenular ophthalmia. He suggests that the phlycten appears only when a hyperallergic phase of this infection is present and there is a suitable (? specific) exciting factor of endogenous or exogenous origin, such as metabolites, tubercle bacilli or tuberculous dust. In fact, the phlycten may be described as a spontaneous tuberculin test reaction, but its significance is more grave than that of an artificially induced positive tuberculin reaction in a child: this is borne out by the subsequent incidence of tuberculosis and mortality from it in children previously affected with phlyctenular ophthalmia. The gratifying fact is that most children with tuberculous infection and phlyctenular ophthalmia overcome the infection and do not develop clinical tuberculosis.

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THE PRODUCTION AND TREATMENT OF EXPERIMENTAL HYPOPYON ULCERS IN THE RABBIT

by J. M. Robson & G. I. Scott, *British Journal of Experimental Pathology*, **24**, 50–56, April 1943

Continuing their studies (Robson & Scott, 1942; 1943) in local chemotherapy on experimental corneal lesions in the rabbit, the authors report, from the Department of Pharmacology, Edinburgh, an investigation of the value of sodium sulphacetamide, sodium sulphapyridine, penicillin and tyrothricin on artificially induced pneumococcal infections. By injecting into the cornea pneumococcus type 19 (a 6 to 15 hours' culture in plain broth) they succeeded in obtaining clearly defined corneal ulcers frequently associated with hypopyon. Definite beneficial effects were obtained with penicillin and 30% sodium sulphacetamide, but especially with the first. Tyrothricin was of little value, and 30% sodium sulphapyridine tended to produce secondary effects by the deposition of the powder. In the use of sodium sulphacetamide, delay for more than 6 hours greatly decreased its value; with penicillin, quite appreciable effects were still obtained when treatment was delayed for 24 hours.

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THE SULPHONAMIDES IN EXPERIMENTAL OCULAR INFECTIONS

by M. Klein & A Sorsby, *British Journal of Ophthalmology*, **27**, 241–254, June 1943

The authors, the second of whom has recently been appointed Research Professor of Ophthalmology at the *Royal College of Surgeons*, give a general survey of the position of both general and local chemotherapy in experimental ocular infections and report a series of experiments which substantiate the value of the sulphonamides for general administration in streptococcal and possibly pneumococcal experimental infections of the interior of the eye. They could not substantiate the value of the sulphonamides for local administration in either streptococcal or *B. pyocyaneus* infections and could not obtain any evidence of the efficacy of the sulphonamides against corneal lesions from *B. pyocyaneus* even when the drugs were given subcutaneously. They stress the need for a more standardised technique of inducing experimental infection of the cornea with the organisms commonly seen, and maintain that the problem of the relative value of the general and local use of the sulphonamides still remains unsolved, and that the value of local therapy is still an open question.

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AVASCULAR HEALING IN THE CORNEA

by B. D. Pullinger & I. Mann, *Journal of Pathology and Bacteriology*, 55, 151–158, April 1943

In this paper from the laboratories of the *Imperial Cancer Research Fund*, London, and the *Nuffield* Laboratory of Ophthalmology, Oxford, the authors report a study of the healing of experimental lesions with liquid dichlorodiethyl-sulphide (mustard gas) in the eyes of rabbits. The same authors (1942) have previously reported on the clinical pathology of such experimental lesions. Spontaneous avascular healing invariably followed when the applications of the liquid droplet damaged the centre of the cornea alone, leaving the corneo-scleral junction uninjured and free from oedema. That healing occurred by sliding down of limbal epithelium was readily observed macroscopically when rabbits which were pigmented at the corneo-scleral junction were used. In the course of healing, the substantia propria was invaded by large numbers of wandering cells, readily demonstrated by the use of vital staining. Some of these cells acted as macrophages, others were transformed into keratoblasts (corneal fibre-forming cells) and fibrocytes, while some probably became corneal corpuscles. The original paper is illustrated by 13 photomicrographs.

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WAR SURGERY OF THE EYE: Removal of Magnetic Intra-ocular Foreign Bodies by the Posterior Route

by H. B. Stallard, *British Medical Journal*, 2, 629–631, 28/11/42

The outstanding problems in the removal of intra-ocular foreign bodies are localisation and method of operative approach. Under war conditions a simple technique of localisation is necessary and the present author advocates a radiological procedure suggested by Brigadier C. W. Graham, consulting ophthalmologist to the British Army in the Middle East.

The principal points of this technique are as follows: The eye is anæsthetised with cocaine, and when it is much inflamed 2–3 minims [0·12–0·2 cm.^{3}] of a procaine solution are injected into the episcleral tissues at the limbus at the 12, 9, and 3 o'clock positions. A silver ring of a size to fit exactly the corneo-scleral junction is stitched in position by sutures of 000 gauge silk passing through the conjunctiva at 12, 9, and 3 o'clock. A drop of liquid paraffin is instilled into the eye, and a pad moistened in the oil is applied to the closed lids and bandaged in position. When possible the patient sits during *x*-ray examination, but in some cases other wounds prevent this. He is directed to look forwards during the first exposure and downwards for the second. For this purpose conspicuous marks such as red disks or lights 5 cm. in diameter are placed on the wall for sitting cases, and on the ceiling for lying cases, at the two points at which fixation of the eyes is necessary during exposure. Each exposure is half the normal. To obtain a postero-anterior view of the orbit free from the dense shadow of the petrous part of the temporal bone the head is tilted slightly so that the occiput is down and the face up; the petrous shadow then falls over the antra. In an accurate postero-anterior radiograph the silver ring shows as a perfect circle, and in the lateral radiograph as a linear shadow.

The interpretation of these radiographs offers no special difficulties. Movement of the foreign body is the essential diagnostic feature. If the relation of the silver ring image to the foreign body is unaltered in the first and second position it may be presumed that the foreign body is moving with the eye. The radiographs with the schematic eye marked upon them will indicate also the position of the object with regard to the centre of rotation. If the foreign body is in front of the centre of rotation it will apparently move with the ring; if it is behind it will move in an opposite direction—that is, a foreign body in the posterior half of the eye will lie at a higher level in the second position where the ring has rotated downwards.

The shadow of the foreign body might fall within the circles described and yet be outside the eye. This point is settled by the movement of the foreign body, which is absent when it is extra-ocular. There is, however, an exception to this in the case of a foreign body in Tenon's capsule, in which case slight movement may take place, but this is rarely as great as in the case of an intra-ocular foreign body.

For removal of foreign bodies the author advocates the posterior route. This has the advantage of avoiding injury to the ciliary body, iris and lens, and is of particular value for non-magnetic foreign bodies—a point of considerable importance, as many foreign bodies arising from missiles used in the present war are non-magnetic. In the author's series the foreign body was visible with the ophthalmoscope in 50 per cent. of cases; in the remainder it was obscured by vitreous hæmorrhage. In such patients localisation must be by radiography. By the use of surface diathermy, 70 to 80 mA for 5 seconds, and a mattress suture (000 silk threaded on a Merson small eyeless needle) passed through half the thickness of the sclera, control of bleeding and controlled exposure of the field of operation is readily obtained. Incision of the sclera and instrumental removal of the foreign body can then be carried out. Operative results by the technique described have been good.

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VITAMIN A AND DARK ADAPTATION

by J. Yudkin, G. W. Robertson & S. Yudkin, *Lancet*, 2, 10–13, 3/7/43

In this paper from the *Dunn* Nutritional Laboratory (Cambridge) and the Department of Chemical Pathology, *University College* (London), the authors describe the technique employed in testing the dark-adaptation of 400 people. The apparatus used was that described by Haines (1938). The subject looks down a tube 14 inches [about 35 cm.] long which is whitened on the inside and is illuminated by a 75-watt lamp. The test is conducted by switching on the bright light and instructing the subject to rest his head against the end of the tube and look along it. After seven minutes the bright light is replaced by a test light and a white plate bearing black arrows pointing in different directions is rotated into place so that one of the arrows is visible. It takes the subject about 20 to 30 seconds to see the arrow, then the intensity of the illumination is still further decreased. This procedure is repeated until 30–40 minutes have elapsed, when dark-adaptation is usually complete. After 30 minutes of adaptation, the threshold is usually determined by a procedure which is the reverse of that used in the earlier part of the test. The minimum detectable illumination is determined by increasing the light until the arrow is just seen and then slowly reducing it until it disappears. This is repeated about three times, after 30 minutes, after 35 minutes and after 40 minutes of adaptation.

Using this technique the authors found that they were able to get results which could be repeated, within narrow limits, for any one individual. They found also that the visual threshold, particularly in the first ten minutes, did not necessarily bear any relation to the final rod-threshold. This observation is important because many people still attempt to assess dark-adaptation by methods which give readings within a few minutes or seconds of the onset of dark-adaptation.

The four possible ways in which vitamin A may affect dark-adaptation are by alteration in:

(i) Final rod threshold only,
(ii) final rod threshold and final cone threshold,
(iii) final rod threshold and cone-rod transition time,
(iv) final rod threshold, final cone threshold, and cone-rod transition time.

In an intensive study on 14 subjects of the effect of vitamin A (24,000 international units daily) and carotene (20,000 international units daily) on dark-adaptation, the authors observed each of the four types of alteration, and these are depicted in the original paper by a series of curves.

When vitamin A has any effect at all it always affects the final rod-threshold. The cone-threshold or the rod-cone transition time may or may not be affected.

One of the main conclusions from these findings is that techniques of assessment of visual performance in the dark must take into account the requirements of the subject.

For those engaged in outdoor night work for long periods,

the final rod threshold is probably of most importance, whereas the cone-rod transition time is of special importance for those who must alternate rapidly between dark surroundings and bright light.

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STOMACH IN HEALTH AND DISEASE

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MOTILITY OF THE FASTING STOMACH IN HEALTH AND DISEASE

by W. F. Anderson, *Lancet*, 1, 40–42, 9/1/43

In this paper from the Department of Materia Medica and Therapeutics of Glasgow University the author describes a modification of Carlson's (1916) balloon method for recording the movements of the empty stomach in man. Objections to this technique are discussed and the author concludes that, after an initial disturbance due to inserting the balloon, mechanical stimulation becomes insignificant and the balloon itself does not initiate contractions. Twenty-three healthy subjects were investigated. Three phases in gastric activity were revealed: (i) period of active contractions, (ii) tonus rhythm, and (iii) phase of relative quiescence. A tetanic phase was not observed in the healthy stomach. The oculo-gastric and carotico-gastric reflexes described by Danielopolu (1930) were demonstrated but if the stomach was quiescent the phase of excitability was not elicited in either reflex. The acid content of the gastric secretion varied from complete achlorhydria to well-marked hyperchlorhydria in these subjects, but the duration of the individual gastric contraction remained practically constant, and the amplitude did not appear to be related to the amount of hydrochloric acid in the gastric juice.

In 10 patients with acute duodenal ulcer, gastric tone was increased while individual contractions were stronger than in the healthy stomach. Occasionally a phase of tetanus was demonstrated. In a patient with acute gastric ulcer the contractions were weak, while in one with chronic gastric ulcer they were powerful. In two patients with gastric carcinoma contractions were less frequent and less powerful than in the healthy subject. In several patients with duodenal ulcer the complaint of a spasm of pain coincided with the appearance of a very marked contraction, in one instance tetanus, of the stomach.

The ingestion of cold water by healthy subjects always inhibited gastric contractions, but in 8 patients with peptic ulceration there was either no change or an increase of gastric motility.

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GASTRIC ACIDITY DURING THE FIRST YEAR OF LIFE

by R. A. Miller, *Archives of Disease in Childhood*, 17, 198–209, December 1942

Until within recent years it has been generally accepted that gastric acidity was low and increased little throughout the first year of life, and that congenital achlorhydria was probably non-existent. In 1938, however, Cutter noted a rapid rise in the gastric acidity during this period by adopting the use of histamine test-meals. Three years later, Miller (1941) showed that the newborn infant had a very acid fasting juice similar in potency to that of an adult, and that the lowest values in infancy appeared only when the infant was at least two or three days old. Out of the 50 healthy babies thus tested there were 6 exceptions who had achlorhydria from birth.

Further evidence confirming and modifying the above findings is supplied in the present paper from the Department of Child Life and Health of Edinburgh University. The author has demonstrated the development in the digestive power of the infant by examining about 200 test-meals throughout the first year of life. These meals consisted of equal parts of milk and water and amounted to sixty minims per pound [approximately 8 cm³. per kg.] body weight. Three specimens of gastric contents were taken; one after the infant had been starved for 3–8 hours, and the other two ½ and 1 hour after the test-feed had been given. The results of these tests may be briefly stated by saying that the average maximum free acidity was 0 cm³. N/10 free acid and 18 cm³. N/10 total acidity at the end of the first week of life, whereas these values rose to 20 cm³. and 61 cm³. respectively by the end of the first year of life. The incidence of achlorhydria during this period fell from 100 % to 17·5 %.

The author concludes that after an infant is a week old and maternal influence is absent, there is a progressive increase in gastric acidity throughout the first year of life which is accompanied by a decline in the number of achlorhydric infants. These changes are primarily due to the making good of a deficiency in the functional capacity of the stomach, and to a less extent to the actual development of the glands in the gastric mucosa. Consequently congenital achlorhydria, no matter whether true or false, is almost always a transitory and not a permanent phenomenon during the first year of life. In addition, it was noted in two cases of pyloric stenosis that gastric stasis and abnormalities in the gastric acidity occurred only after the onset of vomiting. Similarly, in seven babies who had suffered from eczema the test-meal results did not differ appreciably from the normal in the early stage of the disease. It is concluded that any change observed in these diseases is not primary but secondary.

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EVALUATION OF GASTROSCOPY

by A. Morton Gill, *Lancet*, 1, 333–334, 13/3/43

The author, from experience gained in an *Emergency Medical Service* Gastro-intestinal Unit [described by Gill, Berridge & Jones, 1942], suggests that a soldier with dyspepsia profits from complete investigation, including gastroscopy, and that it does not aggravate his symptoms. The soldier accepts the results, and further investigation is rarely required or justified. In order to substantiate this latter claim the results of 1,000 consecutive gastroscopies on service cases are analysed in the present paper.

Analysis of Material. The cases have been divided into 3 groups, A, B, and C, in accordance with the radiological findings.

Table of Gastroscopic Findings

	Whole series		*Group*		
	No.	%	A	B	C
Normals	295	36·6	60	164	71
Ulcer, including benign pyloric stenosis	43	5·3	34	9	0
Gastritis:	396	49·1	201	102	93
Superficial	*196*		*89*	*63*	*44*
Hypertrophic	*166*		*98*	*21*	*47*
Atrophic	*34*		*14*	*18*	*2*
Postoperative	6	0·7	6		
Tumours	4	0·5	2	1	1
Miscellaneous	51	6·3	19	22	10
(the largest group here is multiple erosions)	*36*		*16*	*15*	*5*
Failures	11	1·3	1	10	0
Total (excluding figures in italics)	806		323	308	175

Group A. Both radiography and gastroscopy revealed a gastric lesion. The gastroscope proved of special value here in ulcer cases to demonstrate that final healing had indeed occurred. In the classification of gastritis and the follow-up of the results of treatment, the gastroscope was also of considerable value. The frequency of gastritis will be seen from the table. In general, the superficial and hypertrophic types do not seriously incapacitate soldiers, but the atrophic type, usually a permanent and progressive lesion, requires invaliding. Multiple gastric erosions occurred most frequently in the miscellaneous group, and although they respond well to treat-

ment, they often relapse. Where relapse occurs after treatment, discharge from the Forces is advised. In 60 cases no lesion was seen at gastroscopy, although a positive *x*-ray finding was reported. Fifty-five of these cases were of gastritis, and 5 were of ulcers, usually high in the antral roof.

Group B. No gastric or duodenal lesion was found at *x*-ray. It was concluded that approximately the same number of ulcers invisible to *x*-ray were not seen with the gastroscope. The cases of atrophic gastritis in this group all presented an achlorhydria or a hypochlorhydria. It may be concluded that gastroscopy is indicated in any chronic dyspeptic, or in men with much diminution of the acid secretion.

Group C. No gastric lesion was found at *x*-ray, but abnormality of the duodenum or pyloric canal was demonstrated. There were few important gastric lesions in this group.

Conclusions. A thousand consecutive gastroscopies in military patients lead the author to the following conclusions: In gastric ulcer cases, the gastroscope affords proof of healing, and reveals ulcers not otherwise demonstrable. In chronic gastritis it provides confirmation of the diagnosis, and differentiates its type and severity. Mucosal atrophy can be diagnosed with certainty only with the gastroscope. Multiple gastric erosions are seen well gastroscopically, and differentiated into acute and chronic lesions. Disposal of patients can be arranged accordingly. The Hermon Taylor gastroscope was used throughout.

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POLYPS OF THE STOMACH AND POLYPOID GASTRITIS

by E. Spriggs, *Quarterly Journal of Medicine*, **12**, 1–49, January 1943

During routine examination, with barium *x*-rays, of 4424 persons at the *Ruthin Castle* Clinic, 30 cases of filling defect were seen, due to pear-shaped or nodular masses in the stomach. These were either true polyps, or multiple polypoid outlines due to hypertrophic œdematous folds. The latter condition differs from the usual hypertrophic gastritis by the presence of large nodular masses. The first group totalled 10, or 0·3 %, of all stomachs examined, and an 11th case of polyp in the duodenum was revealed at operation. The second group totalled 19 cases, and 470 patients were found to have gastritis during the same period. The author discusses this series of cases, together with 35 cases of gastric polyps communicated by colleagues, and 54 from the literature.

Pathology. Benign gastric tumours may be papilloma, adenoma, leiomyoma, adenomyoma, neuroma, angioma, lipoma, angio-endothelioma, or cysts. They are usually adenoma or papilloma, leiomyoma, and the polypoid hyperplasia ascribed to chronic irritation.

(i) The papilloma or adenoma may be single or multiple, sessile or stalked. It may be tree-like, and is usually small. The epithelial element may become carcinomatous. This occurs in about 1 in 5–6 cases, considerably less often than in intestinal polyadenoma.

(ii) Leiomyoma is usually single, and may be large. Sarcoma may follow. Ulceration leading to hæmorrhage is not infrequent.

(iii) The hyperplasias are usually the result of a chronic gastritis which at times produces hypertrophic polypoid masses. These appear red and convoluted through the gastroscope.

Polyps : The diagnosis is made radiologically and gastroscopically. The frequency was 0·25 % of patients examined, amounting to 11 cases, and in the same series there were 102 carcinomata, and 5 % of persons had peptic ulcer. The epithelial types of polyp were commonest, followed by the polypoid myomata. The commonest site was the body and pre-pyloric part of the stomach. The average age was 55, and the sex distribution appeared to be equal. About half were single polyps, the rest multiple.

Symptoms in 100 Patients with Gastric Polyps

Gastric pain	51	Weakness	17
Eructation	12	Wasting	17
Vomiting	21	Diarrhœa	8
Nausea	12	Constipation	4
Hæmorrhage and anæmia	33	Anorexia	8
		Palpable tumour	9

Treatment. Where there is hæmorrhage or persistent dyspepsia, or the polyp is large, a wide excision of the tumour and its base is desirable, *i.e.* a partial or subtotal gastrectomy. The patient's condition must of course be suitable, and preoperative treatment including transfusions may be required. Patients with polyps which are causing no symptoms, or symptoms which yield to medical treatment, or patients unfit for operation, have been under observation for years without mishap. Patients with polyps do not usually die of them.

Polypoid Gastritis : The process is not neoplastic, nor does it give rise to tumour formation. In the author's series of 19 cases, there was gastroenterostomy, or past or present peptic ulceration in 7. In 3 of the remaining 12 there was evidence of alcoholic excess. Swallowed septic material was an obvious cause in 1, and a probable cause in 2 others.

Diagnosis is again radiological, and is confirmed with the gastroscope. Some of the masses resemble carcinoma. Clinical features of carcinoma are, however, absent, and no tumour can be felt. Radiologically the flexibility and power of contraction of the stomach are characteristic. Dyspepsia is invariable and has an inconstant food relation. In cases without ulceration, the free HCl was low or absent. In these cases there was degeneration in the gastric epithelium. In 3 patients, progress towards achlorhydria was noted over 2–5 years, and was compatible with clinical improvement.

Treatment. After hæmorrhage, an early gastric ulcer diet is needed, with eggs and milk. Otherwise the amount, nature, and frequency of feeds to be prescribed are individual matters, particularly with achlorhydria. The patient's experience is a valuable guide. Fruit purée and green vegetables are good, and alcohol is best avoided.

Gastric lavage is valuable. A tube may be used, or self-lavage by drinking a pint of water containing a teaspoon of sodium bicarbonate.

The regime prescribed appears to have assisted in promoting regression of symptoms and swellings.

The original 49-page paper contains case-histories, a tabulated summary of the findings in a large number of cases, drawings in colour of gastroscopic and microscopic appearances, radiographs, and drawings and photographs of macroscopic appearances.

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HÆMATEMESIS AND MELÆNA: With Special Reference to Bleeding Peptic Ulcers

by F. Avery Jones, *British Medical Journal*, **1**, 689–691, 5/6/43

The author, who is physician in charge of the dietetic wards of the *Central Middlesex* County Hospital, reports a full investigation of 171 cases of hæmorrhage from stomach or duodenum. Accurate records were obtained both of the cause of the bleeding and of the results of treatment with large transfusions and early feeding.

It is unsatisfactory to look only at an *x*-ray shadow when the ulcer can be directly inspected through a gastroscope. Gastroscopy was performed on many cases within a week of bleeding. This did no harm, and in 21 cases ulcers were found which had not been diagnosed clinically or radiologically. Consequently a high standard of diagnostic accuracy is claimed for this series. The final diagnoses are shown in the table on p. 109.

Out of these 171 cases there were 17 deaths. This 10 % mortality at first seems high compared with other series such as that of Miller & Nicholson (1941) who reported a 3·1 % mortality in 1396 cases, but allowance must be made for the large number of old people in the present series (30 % were over 60 years of age).

	Admissions			Deaths
	No.	Male	Female	
Chronic lesser curvature ulcer found by *x*-ray, operation, or necropsy	30	26	4	7
Acute gastric ulcer found by early gastroscopy but not visible when radiographed later	21	15	6	0
Acute gastric ulcer found at necropsy	1	0	1	1
Pyloric ulcer	2	2	0	0
Chronic gastric and duodenal ulcers	5	4	1	0
Duodenal ulcer	47	36	11	3
Duodenal ulcer with gastro-enterostomy	6	6	0	0
Jejunal ulcer (gastro-enterostomy)	2	2	0	0
Localized jejunitis	1	1	0	0
Probable peptic ulcer with thoracic stomach	2	0	2	0
Peptic ulcer of Meckel's diverticulum	1	1	0	0
Hæmorrhage complicating perforated gastric or duodenal ulcer	7	6	1	3
Acute gastritis	2	2	0	0
Carcinoma ventriculi	4	2	2	0
Leiomyoma ventriculi	1	1	0	0
Portal thrombosis—gastrostaxis	1	1	0	1
Cirrhosis hepatis	4	1	3	2
Uncertain (6 patients not investigated)	34	21	13	0
Totals	171	127	44	17

Treatment

(*a*) Diet: The patients were given 2-hourly purée feeds, and were allowed to drink an unlimited amount of $\frac{1}{3}$-normal saline between feeds.

Purée Diet

6 a.m.	Cup of milky tea
8 a.m.	Porridge and bemax; thin bread-and-butter and jelly marmalade; cup of milky tea
10 a.m.	Cup of milk and biscuit
12 noon	Minced meat, chicken, or steamed fish; mashed potato; purée carrot or cauliflower
2 p. m.	Egg custard or cereal pudding or apple purée; orange juice
4 p.m.	Cup of milky tea; three slices of thin bread-and-butter; fruit jelly; sponge cake
6 p.m.	Vegetable soup or minced chicken sandwich
8 p.m.	Milk pudding or cup of milk
10 p.m.	Cup of milk and biscuit

Milk feeds during the night if awake

(*b*) Transfusion: Without any rigid rule, blood was usually transfused when the pulse rate remained above 120 per minute, the blood pressure below 90 mm. Hg, or the hæmoglobin below 40%, but any case whom further bleeding might endanger was transfused. With the *Medical Research Council* transfusion apparatus, exposure of the vein was rarely necessary, and both the patients' vessels and the nursing staff were therefore left unperturbed. The blood was given at a rate of 40 drops per minute, or faster in exsanguinated patients. The total amounts usually varied from 1–5 litres. Morphine $\frac{1}{6}$ grain [about 10 mg.] was given when bleeding occurred. Iron and ascorbic acid were given afterwards.

Discussion

In a comparable series of cases treated with *restricted* fluids and *scanty* transfusions (Cullinan & Price, 1932) the death rate was twice that of the present series, and recurrent hæmorrhages more frequent, as is shown in the following table:

	Cullinan & Price	*Present Series (Hæmatemesis cases only)*
Number of cases with hæmatemesis	105	126
Deaths	19	10
Recurrent Bleeding	39	35
Recurrent bleeding and death	16	6

There is thus good evidence favouring the present treatment.

Surgical Treatment

In diagnosed cases only those with chronic gastric ulcers or perforations showed any indications for surgical intervention (which carries a 26% mortality). The dangerous chronic ulcers were those associated with old age, arteriosclerosis, severe pain, or recurrent bleeding, and such cases could possibly be saved by expert surgery. In undiagnosed cases the same indications apply, but the necessity for continued transfusions is no reason for operation.

Organisation

Successful results demand a special diet ward, a staff experienced in this treatment, and an adequate blood bank. Intractable ulcers detected in the follow-up clinic should have partial gastrectomy before complications occur.

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CARDIOVASCULAR SYSTEM

174

SIGNS SIMULATING THOSE OF MITRAL STENOSIS

by C. Bramwell, *British Heart Journal*, 5, 24–26, January, 1943

The purpose of this paper from the Cardiographic Department of the *Manchester Royal Infirmary* is to suggest that duplication of the second heart sound at the apex is physiological. Also to put forward a hypothesis to account for this, and for certain other signs that may lead to a mistaken diagnosis of mitral stenosis.

The duplicated second sound is best heard with the patient lying on the left side. This is due to the horizontal and therefore accelerated blood-flow from auricle to ventricle. The second element of the duplication appears to be identical with the physiological third heart sound. Both occur more commonly in young subjects. In 43% of a series of recruits a duplicated second sound was heard, and 70% were fit for service in grade one. Radioscopy usually showed a prominent pulmonary arc. The duplicated second sound was usually associated with a frank apical systolic murmur, or an impure first sound. This murmur may be attributable to a safety-valve mitral incompetence, associated with ventricular over-filling. This is similar to the murmur heard in normal people after severe physical exertion.

Presystolic Murmur. The presence or absence of this murmur is determined by the velocity of the blood-flow through the mitral orifice, not by its size. The author suggests that even with a normal-sized orifice, sufficient increase in the rate of blood-flow will produce a murmur. In the course of a routine examination of 192 long-distance athletes at the Olympic Games it was found (Bramwell & Ellis, 1931) that 12 had a modified first sound indistinguishable from a presystolic murmur. The increased blood-flow may be caused by auricular hypertrophy (part of the general cardiac hypertrophy) in athletes, or in an excitable over-acting heart, as in thyrotoxicosis. In both cases there is a relative mitral stenosis due to increased blood-flow.

Early Diastolic murmur. The classical signs of mitral stenosis are a presystolic murmur, with an accentuated first sound, and a duplicated second sound, in the early stages of the stenosis. Later the duplicated second sound is followed by a diastolic murmur. The second element of the duplicated second sound is due to vibrations of the thickened mitral valve set up by the first rush of blood from the auricle into the ventricle.

In this respect its mode of production is similar to the normal third heart sound. But in the former the sound is attributable to stenosis of the orifice and thickening of the cusps, and in the latter to an increase in rate of blood-flow with a normal valve. The former is the pathological, the latter the physiological, third heart sound.

The author's hypothesis entails a physiological conception of mitral stenosis based on the volume of blood which an orifice of a certain size can transmit in unit time.

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CARDIAC SYMPTOMS COMPLICATING DIABETES AND THEIR TREATMENT

by K. S. Smith, *British Heart Journal*, 5, 1–7, January 1943

The author, who is physician to *Charing Cross* Hospital and the *London Chest* Hospital, records observations on 49 patients

with diabetes and heart disease, discusses the nature of the cardiac syndromes developing, and outlines schemes of treatment.

There is much evidence in the literature to suggest that diabetes is conducive to early and serious heart disease, *e.g.* Root, Bland, Gordon & White (1939), in necropsies on 349 diabetics and 3,400 non-diabetics, found coronary occlusion in 23% of the diabetics and 6% of non-diabetics between 40 and 60 years of age. Other observers have shown general and aortic sclerosis and hypertension to be common in diabetics.

Clinical Observations in the Present Series

The 49 diabetics with heart disease suffered from all grades of diabetes. The heart disease ranged from symptomless hypertension to acute coronary occlusion. Average age was 61 in females and 62 in males and the sex distribution was even. Disease of the heart was always hypertensive or degenerative. 41 cases exhibited hypertension, and the pressure fell considerably under treatment.

Relation of Cardiovascular Disease to Diabetes

Group 1. Patients known to have diabetes and cardiovascular disease: 18 cases. The diabetes is usually of long duration, and coronary thrombosis is common.

Group 2. Patients known to have diabetes, and developing heart disease: 12 cases.

Group 3. Patients known to have heart disease, and developing diabetes: 5 cases.

Group 4. Patients previously believed well, in whom the occurrence of a cardiac or diabetic syndrome brought to light the presence of diabetes or heart disease: 14 cases.

Various Cardiac Syndromes

(i) Effort angina and spasmodic angina: Angina may be of the usual type associated with coronary sclerosis, or it may be related to metabolic disorder of the heart-muscle (in which case improvement may follow insulin treatment).

(ii) Coronary thrombosis and cardiac infarct: The incidence of this is highest amongst diabetics needing, but not taking, insulin, although the latter are not protected from coronary thrombosis. The sudden withdrawal of diet or insulin may precipitate coronary thrombosis.

(iii) Cardiac asthma and congestive heart failure: In diabetics the disturbance of cardiac nutrition may determine the development of failure, and stabilisation may improve the circulation.

Treatment of Cardiac Diabetics

In general it is safer for these patients to live with a moderate hyperglycæmia and have glycosuria from time to time, than for them to be controlled more strictly. The myocardium may depend for its nutrition upon hyperglycæmia compensating for the deficient coronary flow.

Diets should restrict foods of high cholesterol content, *e.g.* eggs, cream, butter, cheese. When heart failure occurs, insulin may need to be increased as the basal metabolic rate rises, especially as fever may coexist. The ferric chloride test should be preferred to Rothera's test. If it is positive, treatment of the diabetes should take preference over the cardiac condition. Increased fluids, insulin and glucose (1 g. per unit of insulin) will then be required. Warmth and rest are essential from all points of view. The combination of coronary thrombosis with diabetic coma is very desperate, and treatment should be directed to the coma. The problem of fluid intake in congestive heart failure is most difficult. It is better to risk the onset of œdema in severe diabetes than to allow progressive hyperglycæmia and ketosis. Consequent œdema can be dispersed later with mercurial diuretics. If coma is present intravenous fluid must be given, signs of dehydration indicating a lack of 10–12 pints [about 5·7 to 7·2 litres] of fluid.

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BLOOD PRESSURE AND OLD AGE

by T. H. Howell, *British Heart Journal*, 4, 143–148, October 1942

Investigators in the past have agreed that a rise in blood pressure is customary after the age of 60, the peak being reached between 75 and 89, but falling thereafter. In the present paper from the *Royal* Hospital, Chelsea [a residential establishment for superannuated Army Pensioners], the author attempts to find some relationship between blood pressure, arteriosclerosis, mental state, and physical condition.

Conditions and Standards. The subjects were 120 tough veterans of the British professional Army aged 65 to 92. Each was classified by blood pressure, state of arteries, renal concentration power, mental state, and physical condition. Weekly estimations of the blood pressure were done, and variations were common. Infections, especially when accompanied by diarrhœa or pyrexia, caused a fall in pressure. Pressure also fell before death, particularly if due to cancer or cardiac failure.

Blood Pressure. A systolic pressure of over 160 mm. was taken as definitely high; this occurred in 42% of the total, and included many of the fittest men in the establishment. Only 8 subjects had a systolic pressure of more than 200 mm. Of those with a high pressure, 33 were active physically and only 12 were slightly incapacitated out of a total of 50. Only 6 subjects had a systolic pressure regularly below 115 mm., and all but 1 of these died of cancer or cardiac failure.

Arteriosclerosis and Mental Condition. Each subject was classified according to the state of his arteries as slightly (+) moderately (++) or considerably (+++) thickened. In no case were the vessels soft. The mental condition was assessed as normal adult, normal senile, or impaired.

The author's findings are summarised in the following tables:—

Arteriosclerosis and Blood Pressure

Arterial Thickening	*Total Number*	*Raised Blood Pressure*	*Lowered Blood Pressure*	*Mentally Impaired*
Slight . .	13	16%	24%	8%
Moderate . .	80	38%	4%	22%
Marked . .	27	66%	20%	32%

Mental Condition and Circulation

Mental Standard	*Total Number*	*With raised Blood Pressure*	*Arterial Thickening* +	++	+++
Adult . .	15	73%	33%	67%	—
Senile . .	78	33%	10%	66%	24%
Impaired .	27	50%	4%	66%	30%

Age, Arteriosclerosis, and Raised Blood Pressure

Age	*Total Number*	*Arteries* +	++	+++	*High Blood Pressure*
Below 70 .	26	20%	65%	15%	40%
70–74 .	33	15%	70%	15%	37%
75–79 .	34	6%	76%	18%	50%
Over 80 .	27	4%	52%	44%	33%

Conclusions. A systolic blood pressure above 160 mm. is common in old age, occurring in half to a third of the cases. Amongst the oldest patients the fittest were those with a high pressure. This suggests that a high pressure is needed to offset the increasing arteriosclerosis of old age. Marked thickening of arteries with a low pressure is associated with a poor physical condition, whilst a raised pressure and thickened arteries are compatible with relative fitness and activity. No man with very thickened arteries had adult intelligence, and no man with impaired intellect had other than at least moderate arteriosclerosis. Measurement of the specific gravity of the urine revealed nothing of significance.

It appears that as arteriosclerosis increases, a greater blood pressure is needed to prevent ischæmia of vital organs. Thus senile hypertension may be compensatory in nature. In its absence, vital ischæmia results in impaired function, either mental or physical.

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BRITISH MEDICAL BULLETIN

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The object of this Bulletin is to provide a guide to medical science and thought in Britain, and it consists mainly of summaries of a representative selection of British papers on subjects of medical interest. Any material appearing in the Bulletin may be published without fee, but acknowledgment of the source, by addition of the initial letters BMB followed by the serial numbers of the items selected, would be appreciated.

SPECIAL CONTRIBUTION

INFECTIVE HEPATITIS

by F. O. MacCALLUM, B.Sc., M.D.

Though jaundice had appeared in epidemic form on a number of occasions in different countries in the 19th century, it was not till 1912 that Cockayne in England pointed out that there seemed to be two forms of infective jaundice, one characterised by a high fever and considerable mortality, the other almost afebrile and relatively benign. The severe form, first described by Weil, was proved to be caused by a leptospira. The benign form consists chiefly of cases of infective hepatitis which may be epidemic, endemic, and perhaps sporadic. There are probably also a small number of cases of true catarrhal and obstructive jaundice, the result of blockage of the bile duct due to a mucus plug or inflammation of its wall. Certain groups of workers, especially in Germany, consider that there is a clinical distinction between these two types of the benign form, and that the catarrhal type is responsible for sporadic cases. This would appear to be a debatable point which can only be solved by an extremely large number of liver biopsies on such cases, or by isolation of a causative agent and an accompanying diagnostic laboratory test.

Distribution of Cases

The disease usually runs a benign course with the majority of cases occurring in children of school age. However, from time to time outbreaks of a more severe type occur which extend to the adult population and may result in an increased number of fatal cases as reported by Wallgren (1930) and Bergstrand (1930) in Sweden.

As in previous wars, this disease has become widely prevalent in the combatant forces. Van Rooyen & Gordon (1942) and Cameron (1943) have described a large number of cases from Libya, Egypt and Palestine. Dietrich (1942), Gutzert (1942), Stuhlfauth (1941), Jacobi (1942) and others have described large numbers of cases among German troops in Occupied Countries and on the various fronts. Ford (1943) has given a good account of an epidemic of hepatitis in the civilian population of England.

Clinical Picture

The signs and symptoms of individual cases and groups of cases may vary considerably, but a composite picture of the disease would be somewhat as follows. The onset is frequently marked by fatigue, headache, loss of appetite and an urticarial or morbilliform rash. Fever, nausea and vomiting, diarrhœa or constipation, and an abdominal pain or a feeling of fullness may occur, as may generalised aches and pains and stiffness of the joints. After these symptoms have lasted for a varying period, jaundice as a rule appears. Alternatively, there may be a free interval before its onset, or it may be the first observed sign. Some cases may have a transient biliuria and never become clinically jaundiced. The patient usually feels much better with the onset of jaundice. In the vast majority of cases the jaundice disappears in one to four weeks, but a few cases may progress to a subacute liver atrophy and an occasional one may die with acute yellow atrophy.

Ætiology and Mode of Transmission

Observations of short and established single exposures made by Booth & Okell (1928) and Pickles (1939) indicate that the incubation period is about 20 to 40 days. The possibility of a longer period under certain conditions must, however, be considered, because cases have been seen in which it appeared that a latent infection had become manifest when the patient's resistance was lowered by another illness or extreme fatigue. The mode of spread has most frequently been considered to be by droplet infection. Some observers in Scandinavia and Germany have favoured the oral route by contaminated water, etc., but no evidence indicating milk, water or food as the source of infection has been forthcoming in Great Britain.

In recent years, cases of clinically similar jaundice have occurred following the use of certain batches of measles convalescent serum, adult serum, mumps convalescent plasma, and yellow fever vaccine which contained serum from apparently healthy adults. In 1937 Findlay & MacCallum first described cases of jaundice occurring in individuals two to seven months after they had been inoculated with certain batches of yellow-fever vaccine. Human serum from normal donors was used in making the vaccine, and hyperimmune serum from recovered cases was given with the vaccine in the majority of instances. None of the sera used could be traced to a donor known to be suffering from jaundice at the time he was bled. All sera were preserved by the addition of 0·2% tricresol, and stored in sealed ampoules at 2° C. Before use the serum was passed through a Seitz K filter and later all sera were heated at 56° C. for half an hour. In 1939, following a close check of all stages in the process, Findlay, MacCallum & Murgatroyd came to the conclusion that the source of the icterogenic agent was probably the human serum which had been introduced into the yellow-fever virus tissue cultures from which the vaccine was made and possibly propagated there along with the yellow-fever virus. This has not been confirmed as yet. Similar incidents on a much larger scale have been reported by Soper & Smith (1940) and Fox, Manso, Penna & Pará (1942) from Brazil, and by the Surgeon-General's Office of the U.S. Army in 1942. In most instances the disease runs a benign course, similar to that seen in infective hepatitis, but a small number of fatal cases have occurred. It has been established that the condition is not a form of yellow-fever itself. At the present moment the most striking difference between the two conditions is the apparent lack of secondary cases among people exposed to individuals with post-vaccine jaundice. The interval between inoculation and onset of illness is also considerably longer than the usually accepted incubation period in infective hepatitis, but this may be related to the route of infection. The most popular view is that serum from an individual in the incubation stage of infective hepatitis has been included in the pool of serum used on these occasions. However, until the infective agent is isolated, the possibility of the disease being caused by some other factor present in certain human sera cannot be ruled out.

Since the introduction of arsenical drugs for the treatment of syphilis, many different clinics have reported cases of jaundice occurring at varying stages of the treatment. In the early days some of this may have been a true arsenical poisoning from impure batches of the drug. However, in later years, retesting of supposedly incriminated lots by animal toxicity tests did not support this hypothesis. Since the last war interest in arsenotherapy jaundice has not been as great as it should have been, but is now revived because of the effects of this disease on military personnel (Mitchell, 1943). Many venereologists consider the problem has been solved by the use of less toxic preparations such as mapharsen (*m*-amino-*p*-hydroxyphenylarsenoxide). On the other hand, many pathologists favour the possibility that as a result of drug treatment the liver is rendered more susceptible to the hypothetical virus of infective hepatitis. Another possibility, as mentioned by Bigger (1943) and others, is that infective blood from one patient is carried to another because of imperfect sterilization of syringes.

Andersen (1937) claims to have infected pigs with material from cases of infective hepatitis in Denmark, but unfortunately a porcine hepatitis was present in the country at the time so that the results are difficult to assess. Siede & Meding (1941), and Siede & Luz (1943) have reported transmission to developing chick embryos. Other workers such as Hoyle (1943), have failed to confirm any of these results or transmit the disease to any laboratory animal. However, Dresel, Meding & Weineck (1943) have recently reported the infection of canaries by inoculating duodenal juice and urine from humans in the preicteric phase of the disease. Experiments with human volunteers have been carried out on a small scale by several workers. Voegt (1942) has reported successful transmission by oral administration of small amounts of duodenal juice and subcutaneous and intramuscular injection of serum and blood from cases of infective hepatitis. Cameron

(1943) injected serum or whole blood subcutaneously in 7 volunteers. Of the 6 he was able to follow, all developed jaundice one to six months later. Recently Oliphant, Gilliam & Larson (1943) have been able to show that the serum of a group of individuals who had developed jaundice following inoculation with icterogenic batches of yellow-fever vaccine, was capable of producing the disease when inoculated subcutaneously into a second group of individuals. A further passage to a third group of normals was possible with the serum of those who developed jaundice in the second group. Serum taken in the preicteric stage was icterogenic, but that taken from one patient 2½ months after the jaundice failed to produce jaundice in 15 inoculated volunteers. The icterogenic agent was not inactivated by heating at 56° C. for 30 minutes, but following exposure to ultra-violet radiation of 2650 Å for 1 hour and 2537 Å for 1½ hours, an icterogenic lot of vaccine failed to produce jaundice in 10 volunteers. As in all previously reported experiments attempts to infect laboratory animals, including the Syrian hamster [*Cricetus auretus*] and cotton rat [*Sigmodon hispidus*], were unsuccessful. In an attempt to prove the infectious nature of so-called yellow-fever-vaccine jaundice, Findlay & Martin (1943) collected nasopharyngeal washings from three patients thought to be suffering from this disease. The washings were instilled intranasally in three supposedly normal individuals, each of whom was said to have developed jaundice after 28, 30 and 56 days respectively. If the yellow-fever-vaccine jaundice is a form of infective hepatitis, it is remarkable that there have not been reports of large numbers of cases of the disease among individuals exposed to these cases. A great deal more work is necessary before any conclusion can be drawn from these experimental results.

Aspiration biopsy of the liver as practised by Iversen & Roholm (1939) and by Dible, McMichael & Sherlock (1943) is a great achievement, helping to clarify our understanding of the underlying histology which had previously been based almost entirely on post-mortem material of cases which developed acute atrophy. The work of Dible and his colleagues in demonstrating a common picture in infective hepatitis, arsenotherapy jaundice and so-called serum jaundice, is especially interesting.

Until the causative agent is isolated and the disease transmitted to a laboratory animal, or some diagnostic laboratory test is discovered, the question of mode of transmission and aetiological relationship of these various conditions must remain largely theoretical.

Treatment

The treatment of the condition has changed somewhat recently, more stress being laid on a high protein as well as on a high carbohydrate content in the diet. As a result of experimental work in certain types of poisoning, such as that of Miller, Ross & Whipple (1940), with chloroform in dogs, it has been considered that proteins with a high content of the sulphur-containing amino-acids, methionine, and cystine, might be of value in the treatment of this condition.

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[4] [*see BMB* **183**] [5] [*see BMB* **179**] [6] [*see BMB* **188**]

Dr. F. O. MacCallum is a member of the staff of the Wellcome Bureau of Scientific Research, where he has been in charge of the production of yellow-fever vaccine since 1940. *He has collaborated with Dr. G. M. Findlay in studies on yellow fever, lymphocytic choriomeningitis, post-yellow-fever-vaccine jaundice, and infective hepatitis. They first reported the occurrence of so-called yellow-fever-vaccine jaundice in* 1937 *and later suggested that the cause lay in the human serum used for making the vaccine.*

Dr. MacCallum is at present Senior Bacteriologist in the team of five selected by the Medical Research Council to study infective hepatitis. The team is working in laboratories in the Department of Pathology, Cambridge University. An intensive and concerted effort is being made to isolate the aetiological agent and find a practical diagnostic laboratory test for this disease.

EPIDEMIC JAUNDICE

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AN OUTBREAK OF EPIDEMIC CATARRHAL JAUNDICE

by L. R. L. Edwards, *British Medical Journal*, **1**, 474–475, 17/4/43

In the past the majority of outbreaks of epidemic catarrhal jaundice in Britain have affected rural areas. It would appear, however, that the town-dweller has little immunity from the disease, as is shown by this report of an outbreak in an urban area.

Sixty-four cases of epidemic catarrhal jaundice occurred among the children and teachers at schools in a large town. The epidemic started in one school, lasting several months, and then appeared after a summer holiday at other schools in the neighbourhood. It began in the spring and extended into the autumn. Both sexes were equally affected. The highest incidences were in the age groups 6–10 years and 20–30 years. The latter group included the school teachers. Eight children in the age-group 4–5 years were affected, 42 between 6–10 years, and 6 between 11–15 years. Of the 5 cases in the age group 20–30 years, 4 were school teachers and of the 2 in the group over 30 years, 1 was a school teacher.

Multiple cases in a family were reported, but no more than 2 cases per family were noted.

The disease spread by contact at school. Groups of 2 or 3 in each class were affected simultaneously, indicating close personal contact and a probable droplet infection. The incubation period was determined to be between 3 and 4 weeks. The infective period seems to be short. The onset was characterised by malaise, anorexia, vomiting, and sometimes upper abdominal pain. Vomiting lasted from a few days to a week and was cyclical in character. Constipation was common at this stage. When vomiting ceased, jaundice appeared in the conjunctivæ and there was some persistent nausea. Skin icterus appeared and spread generally. The urine became orange-coloured and the stools greyish or "clay-coloured." Pyrexia was variable, but headaches were often severe. The liver and spleen were enlarged. The icterus lasted from 2 days to 2 weeks. The urine and fæces became normal slightly in advance of the disappearance of icterus. The adults noted severe pains in the back, arms, and legs. Neither rashes nor skin itching were observed. On recovery, the appetite was excessive. The blood films from 5 of the cases showed a leucopenia with a relative increase in monocytes.

There seems to be no effective measure of control, school closure merely leading to scattering of the disease over a wider area. The period of two weeks' isolation which was enforced during this outbreak seems to be adequate, as it was not followed by any return case.

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INFECTIVE HEPATITIS: 300 Cases in an Outer London Borough

by J. C. Ford, *Lancet*, **1**, 675–678, 29/5/43

An extensive outbreak of epidemic catarrhal jaundice occurred over a period of 7 months in a London suburban area. The focus of the outbreak appeared to be the school population. Three hundred cases were studied. In one school with 778 pupils, 78 cases appeared among the pupils and 2 among the teachers, a total incidence for pupils and teachers of about 10%. One class showed an incidence of 18%, and this included the teacher. The sexes were about equally affected. 80·3% of the cases were in children under 15 and 89·4% were in individuals below the age of 24. [*Compare* Edwards, 1943] The epidemic started in October, 1942, and rose to a peak (102 new cases) in January, 1943. In April, 1943, new cases were appearing at the rate of 9 a week.

Multiple cases, more than 1 per household, numbered 34% of the total cases reported. The incidence of cases to total individuals exposed to contact was highest (28%) in the age groups 5–15 years. Under 5 years and over 15 years it varied between 1·8% and 2·7%. The incubation period was between 14 and 36 days. The prodromal period was characterised by malaise, mental depression, drowsiness or irritability. Headaches, photophobia, shivering attacks, and upper abdominal pain were also observed. Muscular tenderness and joint pains were noted in a few cases. Pyrexia of up to 101° F. [about 38·3° C.] with nausea and vomiting appeared 3–4 days after the onset of the prodromal symptoms, and within 48 hours of these more severe symptoms icterus appeared in the conjunctivæ, spreading rapidly over the skin. The urine was dark and the stools were clay-coloured. The liver was enlarged and there was a rapid loss of weight. When appetite returned, the patients ate ravenously. On the whole, the cases were of a mild type, the jaundice clearing in 1–3 weeks. One death from acute yellow atrophy of the liver occurred.

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INFECTIVE HEPATITIS

by J. D. S. Cameron, *Quarterly Journal of Medicine*, **12**, 139–155, July 1943

Infective hepatitis has been prevalent in Palestine and the adjacent countries for many years in sporadic form among the civilians, especially adolescents, children, and new immigrants. Small numbers of cases were noticed in British troops stationed there in 1938 and 1939, and the disease assumed epidemic form in 1940. Three hundred and forty-two cases were notified in that year and a further 126 cases in 1941. The work reported in the present paper was carried out at two Army General Hospitals in Palestine in collaboration with Professor I. J. Kligler, of the Hebrew University (Jerusalem), Captain D. G. Colville and Major J. L. Dales of the Royal Army Medical Corps, and Captain Hynds of the Royal Army Veterinary Corps.

The signs and symptoms as seen from the clinical records of 170 patients, all of whom became jaundiced, were the same as those described in previous epidemics from other countries. Detailed studies of close contacts of all patients suggested a tentative minimum incubation period of 32 days. It was found that in many cases a much longer incubation period must be considered if the contact assumed to be the source was correct. The hypothesis was made that in such delayed cases the liver was resistant at the time of infection, but later became suitable soil because of some accessory factor such as alcohol, other illness, chill, low diet or fatigue. There was a heavy incidence of the disease following periods of active service in the field.

Numerous attempts to infect experimental animals with blood and nasal washings were unsuccessful.

Inoculations were carried out on 7 human volunteers. The first man received 1 cm.^{3} of unfiltered serum intramuscularly, the serum being obtained from an apyrexial case of infective hepatitis on the 2nd day of jaundice. Symptoms of anorexia, headache and depression appeared on the 30th day, followed by fever and pain in the back, and jaundice on the 35th day.

Blood and nasal washings from this man were injected into a second volunteer, who was still well after 6 weeks, at which time he ceased to be available for observation. Five other men received injections of 1 cm.^{3} serum or 2 cm.^{3} whole blood from cases of infective hepatitis in the pyrexial stage. One felt unwell and passed dark urine 1 month after injection. He recovered from this, but after a further 5 months became jaundiced. A second man developed jaundice 2 months after inoculation, and the remaining three men within 6 months. A number of other cases of infective hepatitis occurred in the same unit, but the incidence was low especially as compared with the 100% incidence in the 6 volunteers.

Attempts to transmit infection from cases of infective hepatitis to human volunteers by bed-bugs were unsuccessful.

The author summarises the *post-mortem* findings in 4 fatal cases and in 1 case in which a piece of liver was removed for biopsy during an operation for intercurrent appendicitis. His main conclusion from the macroscopic and microscopic appearances was that "a generalised infection damages blood-vessels, leading to hæmorrhages, and especially to liver damage resulting in necrosis."

JAUNDICE AFTER ADMINISTRATION OF HUMAN BLOOD PRODUCTS

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HOMOLOGOUS SERUM JAUNDICE: Memorandum Prepared by the Medical Officers of the Ministry of Health

Lancet, **1**, 83, 16/1/43

Jaundice following the injection of homologous serum in man has been reported from time to time. In Brazil, in 1939, 304 cases of jaundice occurred in patients who had received yellow fever vaccine which contained human serum, and this complication recurred in 1940. Further interest in this syndrome was stimulated by the occurrence of 28,585 cases of jaundice in North American troops who had received yellow fever vaccine containing human serum, and the question arose as to whether the widespread use of human serum and plasma for transfusion purposes might be introducing the hazard of this type of jaundice, which in some cases has produced the death of the patient with widespread liver necrosis.

Little had been heard in Britain of this condition except that, in 1937, 41 of 109 recipients of a single batch of measles convalescent serum, administered subcutaneously, developed jaundice, and 8 died. These cases were scattered proportionately over a wide area in the South of England. A batch of measles adult serum, pooled and filtered through a Berkefeld candle in the same laboratory, gave rise to at least 11 cases of jaundice with one death (*Chief Medical Officer*, 1937).

The Memorandum reviewed here was therefore prepared by Medical Officers of the British Ministry of Health to see if any light could be thrown on the subject.

In their survey they discovered that in 1885 there had been an outbreak of jaundice in Bremen following the use of "glycerinated humanised" vaccine lymph (Lurman, 1885). They also discovered that, in 1942, 86 of 266 British troops who had had 14 cm.^{3} of Seitz-filtered pooled mumps convalescent plasma had developed jaundice, and also that of 36 patients who had received large doses of pooled and dried serum for various vascular diseases in an *Emergency Medical Service* hospital, 8 had developed jaundice.

As a result of their survey the authors consider that, although the cardinal sign of the condition is jaundice, it is probable that the disorder occurs without the appearance of jaundice, and they cite the case of a child who, after receiving an otherwise implicated serum, died of "meningismus" some twelve weeks later. The intensity of the jaundice and the liver damage has varied from fulminating liver necrosis to a relatively mild disease. They suggest that differentiation from epidemic hepatitis may be possible, as erythema multiforme, stiff joints and splenic enlargement may be recognised as distinguishing points. A particularly characteristic feature has been the very long latent period between the injection of the human blood products and the appearance of jaundice. This period is commonly between 60 and 90 days.

Tests of sera that have been known to cause the condition have so far shown nothing. As possible causes the authors tentatively suggest a virus, or a mysterious antigen, or a sensitising serum from a sensitive donor.

They also state that analogous conditions in horses following the introduction of homologous serum are by no means uncommon. The most interesting case recorded is that of Stagsvold (1938), who prepared anti-anthrax serum from horses and cows and injected either homologous or heterologous serum into both. Acute or subacute necrosis of the liver occurred in 4% of the horses receiving homologous serum, while the cows treated with either serum and the horses treated with heterologous serum were not affected.

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JAUNDICE FOLLOWING ADMINISTRATION OF HUMAN BLOOD PRODUCTS

by H. V. Morgan & D. A. J. Williamson, *British Medical Journal*, **1**, 750–753, 19/6/43

Between August, 1941, and June, 1942, 56 patients in two associated hospitals were transfused with liquid pooled human plasma or reconstituted dried human serum. The quantity administered varied between 300 cm.^{3} and 6 litres. None of the cases was acutely ill. All were suffering from peripheral vascular disease or hypoproteinæmia. Immediate reactions such as pains in the back, nausea, rigors and pyrexia were not related to the occurrence of jaundice. Of the 56 patients transfused, 50 were traced and 9 had become jaundiced between 49 and 107 days after the last transfusion.

Contact with cases of infective hepatitis during the stay in hospital and after returning home had not occurred. In a ward of 32 patients, one case developed jaundice 68 days after the last transfusion. Five weeks after the onset of symptoms in this case, another patient became jaundiced. The lapse of time since the last transfusion in the latter case was 87 days. At the same time there was in the ward another patient who three and a half months later developed jaundice. The length of time between this patient's last transfusion and the onset of his jaundice symptoms was 107 days.

The onset of illness was sudden. Malaise, nausea and epigastric discomfort preceded the jaundice in 3 cases. One case showed a pre-icteric rash. Neither joint pains nor biliary colic were noted. The liver was enlarged in 8 cases and the spleen in 1. The severity of the disease varied from a symptomless jaundice to one severe case. Most were of moderate severity. The severity of the condition bore no relation to the amount of plasma or serum administered. The illness lasted 3–12 weeks.

The ages of the patients varied between 31 and 62 years. This is in striking contrast to the usual age incidence of infective hepatitis (5–15 years). The illness was more severe than the infective hepatitis recorded in school children, and it lasted longer. There were no relapses. Albuminuria and polymorphonuclear leucocytosis were absent.

The authors consider that the common factor in all their cases was the use of transfusion fluids. They put forward the following hypotheses:

(i) That the condition may be due to an allergic reaction. As there was no evidence of any previous allergic phenomena and no evidence of eosinophilia, this is unlikely. The long time interval between transfusion and the appearance of symptoms is against an allergic reaction.

(ii) That a hepatotoxic agent had been introduced with the transfusion fluid. Such an agent might be either:

(*a*) a virus contained in the fluid, or

(*b*) a toxic chemical substance such as altered plasma protein.

(iii) That the transfused fluids might be toxic to the liver, thus reducing its resistance to the virus of infective hepatitis. The absence of infectivity and the long symptom-free period are against such an explanation.

[Although the authors conclude that a specific virus or an unknown chemical substance is responsible for their cases, their observations in themselves do not suffice to favour one or other of these two views. Recent papers by other observers, however, make it clear that the long symptom-free period between transfusion and the onset of jaundice is compatible with the transmission of a virus by direct inoculation into the blood stream.]

JAUNDICE AFTER YELLOW-FEVER IMMUNISATION

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JAUNDICE FOLLOWING YELLOW-FEVER IMMUNISATION: Transmission by Intranasal Instillation

by G. M. Findlay & N. H. Martin, *Lancet*, **1**, 678–680, 29/5/43

The nasal washings from 4 individuals with icteric or pre-icteric symptoms following yellow fever immunisation were collected and instilled into the 4 human volunteers within 1 hour. The volunteers came from a semi-closed community of 500 individuals in which no case of infective hepatitis (epidemic catarrhal jaundice) had appeared during the previous 10 months. All had been immunised against yellow fever from a batch of vaccine which had not produced a case of post-vaccinal jaundice. None of the volunteers had ever suffered from jaundice.

Donor A developed malaise, loss of appetite, and nausea, 80 days after yellow-fever inoculation. Two days after the onset, his nasal washings were instilled into recipient T. P. Three days after taking the nasal washings, donor A developed jaundice. He had a very mild attack which cleared 26 days after the onset of symptoms. Recipient T. P. complained of malaise, nausea, and upper abdominal pain 30 days after the instillation of nasal washings. His temperature was 100° F. [about 38° C.] and his liver and spleen were just palpable. Stools were light grey in colour. Urine contained neither bile nor albumin, but the serum icteric index rose from 4 to 6. Three days later the icteric index rose to 8, the van den Bergh reaction was a delayed direct positive, urobilin and bile with a trace of albumin were present in the urine. A month later the urine contained only a trace of albumin.

Donor B developed diarrhœa, tiredness, loss of appetite, nausea, and headache, and upper abdominal pain 81 days after yellow-fever vaccination. Three days after these symptoms appeared, nasal washings were taken. On this day his urine contained bile, and in the evening his temperature was 100·2° F. The following day the conjunctivæ were jaundiced, the urine contained bile and a trace of albumin. Two days later the liver was just palpable and icterus was present in the skin. The icterus was fading 48 hours later and appetite had returned. Discharge from hospital took place 8 days later, with jaundice cleared and no bile or albumin in the urine. Recipient J. D. who received the nasal washings complained of constipation and upper abdominal tenderness 50 days after instillation. The liver and spleen were not

enlarged. Six days later the temperature was raised to 100° F. [about 38° C.] and icteric staining of the conjunctivæ was noted. The urine contained bile and albumin. The following day the icteric index had risen to 20 and the van den Bergh reaction was a positive direct. The bile content of the urine had increased and albumin was still present. Four days later the icteric index fell to 18, bile was still present in the urine, but albumin had disappeared.

Donor C on the 83rd day after yellow-fever inoculation complained of loss of appetite, nausea, and malaise. Three days later the urine was dark. Jaundice appeared on the 6th day after the onset. The following day, when nasal washings were taken, the jaundice had deepened and the urine contained bile but no albumin. No enlargement of liver or spleen was present. Stools were pale. Fifteen days after the onset the jaundice was still deep orange. Appetite was poor and nausea was marked. Improvement commenced and on the 35th day of disease he was discharged. Bradycardia was observed from the 11th to the 24th day of the disease. Recipient M. M. developed malaise, loss of appetite and tiredness 28 days after instillation of the nasal washings from donor C. The urine and the van den Bergh reaction of the serum were normal. Temperature was 99·2° F. [37·2° C.] in the evening. Two days later urobilin and a trace of bile in the urine were observed. The serum gave a weak positive direct reaction. The general condition was then improving. No icterus appeared.

Donor D was admitted to hospital 76 days after yellow-fever inoculation. He complained of diarrhœa and vomiting with a slight pyrexia. Nasal washings were taken on the 6th day after admission. He never developed jaundice nor did he show any abnormal urinary constituents. As it was thought he might have been in a pre-icteric state, the washings were instilled into recipient A. Y. This recipient did not develop any illness. On the 56th day his urine had a minute trace of urobilin, but no bile or albumin. His icteric index remained within the range 2·5–3·5.

These experiments show that the infective agent, when injected in the course of the yellow fever inoculation, required an incubation period of 80–83 days for symptoms to appear. When instilled into the nasal cavity, the incubation period fell to 30 days in recipient T. P., 50 days in recipient J. D., and 28 days in recipient M. M. Recipients T. P. and J. D. had obvious jaundice, while recipient M. M. had a subclinical icterus. Donor D. never developed any symptoms of infective hepatitis, nor did the corresponding recipient A. Y. From the evidence of these experiments, it would appear more likely that infective hepatitis is caused by a virus than by a hypothetical toxin.

ARSENOTHERAPY JAUNDICE

184

JAUNDICE IN SYPHILITICS UNDER TREATMENT: Possible Transmission of a Virus

by J. W. Bigger, *Lancet*, **1**, 457–458, 10/4/43

The most probable cause of jaundice after the inoculation of human blood, plasma, or serum is the transfer of a virus from donor to recipient. It may well be that the high incidence of jaundice in syphilitic patients treated by injections of arsenicals is due to the transfer of the same or a similar virus from patient to patient. In venereal disease clinics, blood is commonly drawn into a syringe before the arsenical solution is injected into the vein, and the same syringe is then used, after washing with sterile water and an antiseptic solution, for injection into another patient. It was obvious that this procedure might permit the transmission of infection from patient to patient.

To test the efficiency of the routine washing of syringes in eliminating infective material from the interior of the syringe, the following experiment was carried out. Into a syringe containing 10 cm.^{3} of neoarsphenamine solution (0·6 g. in 10 cm.^{3} of sterile water), about 0·2 cm.^{3} of citrated blood heavily infected with staphylococci was drawn. The contents of the syringe were expelled through a sterile needle, and after removal of the needle the syringe was washed out by filling and expelling in succession two syringefuls of sterile water, one of 0·1 % biniodide of mercury solution and two syringefuls of sterile water. Each washing was drawn from a separate sterile container. Finally, 10 cm.^{3} of sterile water was drawn into the syringe and, after fitting a sterile needle, 4 inoculations (5 cm.^{3}, 2 cm.^{3}, 2 cm.^{3}, and 1 cm.^{3}) into blood culture bottles were made. Each bottle after incubation contained living staphylococci. It was clear that the biniodide of mercury was valueless as an antiseptic under the conditions of the experiment.

Seven further experiments were carried out, identical with the above, but omitting the biniodide washing. Six washings with sterile water were made and inoculations of 1 cm.^{3} were made from the second and subsequent washings. The number of organisms per cm.^{3} in the infected blood was estimated. If the original organism content was 3 million bacteria per cm.^{3}, the first washing ought to contain 1,800, the second 14, and the third and later washings 0 per cm.^{3} It was found that the experimental results did not agree with the expected concentrations and that the content was higher. This was due to the fact that the piston did not fit the barrel so tightly as to scrape the surface free of the fluid previously contained in the barrel. The looser the fit of the piston, the higher the bacterial content of the washings, and the possibility of a hypothetical virus being transmitted from patient to patient by an infected syringe is evident. An effective method of preventing such transmission of infection in departments treating large numbers of patients is not easy to suggest. The ideal of a freshly boiled syringe for each patient may be difficult to put into practice. The use of frequent washing from separate pots of sterile water followed by soaking in a powerful disinfectant and further washing is less satisfactory. Another suggestion is that a glass bulb should be interposed between the syringe and the needle. Blood would flow into the bulb, and with care would not reach the syringe. This method inspires less confidence than washing followed by boiling between injections.

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JAUNDICE IN SYPHILITICS

by J. Marshall, *British Journal of Venereal Diseases*, **19**, 52–58, June 1943

The incidence of jaundice has increased remarkably since early 1941. Of a total of 940 syphilitics attending 3 centres at the time of writing, 273 (29 %) had had jaundice. The author has not, chiefly owing to movements of patients from one region to another, been able to keep accurate comparative statistics. During the relevant period there was no change in treatment, which consisted, for early syphilis, of a minimum of 4 courses of 10 weekly injections of neoarsphenamine (0·6 g.) and bismuth (0·2 g.), with an interval of 4 weeks between courses.

Hepatitis, with or without jaundice, can occur at any stage of untreated congenital and acquired syphilis. In congenital syphilis enlargement of the liver is not uncommon, but clinical jaundice apart from treatment is rare. The mild hepatitis of primary and secondary syphilis gives rise to clinical jaundice only in 0·1–3·0 % of patients. In most cases it is coincident with a severe florid secondary syphilis, and arsenical treatment usually clears up the condition. Acute yellow atrophy has been noted in untreated cases but is apparently rare. In late syphilis, liver involvement is rare.

Liver dysfunction occurring during arsenical treatment can be classified in four main types:

(i) Acute or mild hepatitis,
(ii) chronic or more severe hepatitis,
(iii) sub-acute yellow atrophy with recovery but followed sooner or later by some degree of hepatic cirrhosis,
(iv) acute yellow atrophy.

Types (i) and (ii) tend towards complete recovery, but type (iv) is usually fatal. The clinical types are not in any way different from those seen in the non-syphilitic population. The mild hepatitis commences with a pre-icteric stage during which the patients complain of anorexia, indigestion, nausea and vomiting. The urine may become dark and the stools pale. This phase may be short and the symptoms so vague and mild that it may pass unnoticed until the urine becomes dark or icterus appears. Joint pains and skin rashes are not uncommon pre-icteric symptoms. Icterus appears at any time between a few days and two weeks after the first symptoms. In a small proportion of cases icterus may not appear, but usually urobilinogen can be demonstrated in the urine, and liver function tests indicate some liver damage. When arsenical treatment is withdrawn but bismuth continued these cases of mild hepatitis clear up in from 1–3 weeks.

Only 80 % of these cases show staining of the skin. Chronic hepatitis of type (ii) differs in severity from type (i) and the various symptoms may persist from 4 to 8 weeks. Recovery is slow and six months may elapse before the patient is well.

Type (iii) cases are uncommon. The patient is usually deeply jaundiced and after one or two weeks becomes seriously ill. Some patients become cholaemic while others develop ascites. Recovery is slow and cirrhosis inevitable. Acute yellow atrophy (type iv) is fortunately very rare.

Treatment has not been successful either in accelerating the speed of recovery or in diminishing the severity of the condition. The best diet should contain plenty of protein and carbohydrates with a minimum of fats. No drug tried has been found of value. During convalescence the amount of exercise permitted should be limited. Soldiers do better on leave at their homes than in convalescent camps where exercise may be too vigorous. Alcohol is contra-indicated for at least 3 months. While recovery is the rule, the ultimate prognosis will remain unknown for years.

It is important to resume arsenical treatment as soon as possible. Heavy doses of bismuth should be continued throughout the course of the hepatitis. Arsenic should not be withheld for more than three months. If treatment is not too seriously interrupted there is no reason to believe that the appearance of jaundice has any effect on the syphilitic prognosis.

Jaundice is commonest about the beginning of the second course of treatment, *i.e.* between the eleventh and sixteenth injections, or the fifteenth to the twentieth week of treatment. The same time incidence is noted whether neoarsphenamine or mapharside is used.

It has not been possible to determine the relevant causal factors in the disease nor what is the method of spread. Men are much more liable to jaundice than women, and soldiers than civilians. Alcohol apparently increases the liability to jaundice. The incidence of jaundice in syphilitics rises with the incidence amongst non-syphilitics but at a much higher level. The frequency of cases is 20–40 times greater in syphilitics than in non-syphilitics.

Attempts to reduce the incidence of the hepatitis have shown that when the dose of the arsenical preparations is decreased there is a fall in the number of jaundice cases, but the findings so far are inconclusive.

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JAUNDICE IN SYPHILITICS

by T. E. Anderson, *British Journal of Venereal Diseases*, 19, 58–62, June 1943

The toxicity of neoarsphenamine preparations is not now regarded as the only factor in the production of jaundice in syphilitics. Nedzel (1942) thought that meteorological factors had some effect in his experiments on rabbits and rats. He noted severe effects with low temperatures and high barometric pressure and also when the temperature or barometric pressure fell rapidly. Whether these factors apply to human cases is, however, not known. The drugs vary in the degree of cutaneous hypersensitivity produced in guinea pigs. When the latter were fed on green (summer) food which had an alkaline ash, their sensitivity to neoarsphenamine was less than when the dry (winter) food was given. Sulzberger & Mayer (1931) considered that this effect was related to the acid-base balance rather than to vitamins. Other workers have shown that racial and constitutional factors are of no import and concluded that sensitivity is specific to the arseno-benzol complex and is independent of the actual toxicity of the compounds used.

It is clear from the work of Messenger & Hawkins (1940) that in dogs a high protein diet is the best protection against liver damage induced by arsphenamine. Later work by Miller & Whipple (1940) showed that the liver injury caused by chloroform increases in amount as the body stores of protein-forming material are diminished. Methionine (a sulphur-containing amino-acid) will protect the liver against damage by arsphenamine (Messenger & Hawkins, 1940).

The incidence of jaundice in the Scottish area in the period 1st July–31st December, 1942, was 10·3 %. The greatest number of these cases occurred in the three months August–October (108 out of a total of 171 cases). The author concluded that the cases observed could not be differentiated from the jaundice due to other toxic infective causes.

In an attempt to detect potential jaundice cases, it was found that routine testing of the urine for excess of urobilinogen was the most valuable method. Excess of urobilinogen appears in the urine many days before any clinical sign of jaundice develops. The detoxicating function of the liver was assessed by Quick's method. Six grams of sodium benzoate were given by mouth. An excretion of less than 3 grams in four hours was taken to indicate an impairment of liver function sufficient to warrant suspension of arsphenamine administration. The possibility of the sodium benzoate causing liver damage on its own cannot be ignored, and repeated administrations of this drug may be dangerous.

The author was able to demonstrate that reduction in the dosage of neoarsphenamine or the substitution of mapharside for neoarsphenamine did not reduce the incidence of jaundice.

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PATHOLOGY OF HEPATITIS

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THE PATHOLOGY OF ARSENO-THERAPY JAUNDICE

by J. H. Dible & J. McMichael, *British Journal of Venereal Diseases*, 19, 102–108, September 1943

PATHOLOGY OF ACUTE HEPATITIS : Aspiration Biopsy Studies of Epidemic, Arsenotherapy and Serum Jaundice

by J. H. Dible, J. McMichael & P. U. Sherlock, *Lancet*, 2, 402–408, 2/10/43

In these two papers from the *British Postgraduate Medical School* the authors report the results of an investigation into the pathology of acute hepatitis in which they continued and amplified the liver biopsy studies begun by Iversen & Roholm (1939) in Denmark. The first paper briefly describes the clinical course and the histological lesions of arseno-therapy jaundice only. The second covers also two groups of patients with epidemic hepatitis and " serum jaundice," and includes a short account of the biopsy technique used by the authors, and a more detailed description of the lesions involved.

Biopsies were performed on the following cases :

	Cases		*Biopsies*	
Epidemic hepatitis	14		18	
Arsenotherapy jaundice	35	56	35	61
Serum jaundice	7		8	

by aspirating a small cylinder of liver tissue into a 2 mm. bore cannula passed transpleurally through an anæsthetised track into the right lobe of the liver. In view of the risk of hæmorrhage in severe cases, however, the authors recommend this technique only for carefully selected patients, and under circumstances in which a possible hæmorrhage can be properly and adequately dealt with.

In spite of a number of facts which make such a belief difficult to accept, venereologists have generally been of the opinion that the jaundice associated with the arseno-therapy of syphilis is due to a toxic action of the drug upon the liver—a form of arsenic poisoning due to a hypothetical idiosyncrasy in those whom it occasionally affects. The observations of Roholm & Iversen (1939), however, demonstrated the essential similarity of the lesions in this form of jaundice with those encountered in epidemic hepatitis, and the fact that certain syphilologists have continued to treat jaundiced patients with arsenicals without further ill effects, also fails to support the arsenic poisoning theory.

Although different ætiological factors may have been involved in the authors' groups of cases reported in the second paper, the histological findings were the same in all three types, and are therefore considered as a whole. Acute hepatitis was definitely present in every case, the histological picture varying in accordance with the severity of the jaundice. The different degrees of intensity of liver damage, which are

illustrated by case histories and photomicrographs of the lesions described, are divided into four categories:

(i) *Severe, acute hepatitis with a diffuse lesion affecting the whole liver lobule,* in which considerable destruction of liver cells, disorganisation of the lobular pattern, and infiltration of inflammatory cells is evident,

(ii) *moderate acute hepatitis with mixed diffuse and zonal lesions,* in which destruction of the liver lobule is less pronounced and infiltration of the portal zones more conspicuous,

(iii) "*zonal*" *limited type of hepatic lesion* representing either a mild hepatitis in which the lobular pattern is not disturbed and liver cell necrosis is at a minimum, or a late condition in a hepatitis which is recovering. In the latter case it may be associated with other chronic changes,

(iv) *chronic residual and fibrotic lesions.*

The frequency with which the various types of lesion were found, in relation to the duration of the disease and the intensity of the jaundice, is illustrated in the following table:

Type of lesion	Duration in weeks			Serum bilirubin (mg. per 100 cm.^{3})
	Under 1	1–2	Over 2	
Diffuse . .	12	2	1	3–17·2 (mean 8·0)
Mixed diffuse and zonal .	7	4	3	2·6–14·6 (mean 8·0)
Zonal . .	9	3	9	Under 1 week, 2·5–6·3 (mean 4·7) Over 2 weeks, 1·1–9·2 (mean 3·3)
Residual fibrosis . .	—	—	6*	—

* Duration 7–26 weeks; only two slightly jaundiced.

While the data are insufficient to follow with certainty the histological evolution of lesions of varying severity from their earliest stages, the authors suggest that, in the early stages, degeneration and autolysis are most severe in the cells about the hepatic vein, and that the leucocytic and histiocytic reaction may proceed from the portal zones centrally.

There are four possibilities as regards the further evolution of the hepatitis:

(i) *Clinical recovery with complete restitution of the liver* may follow even severe diffuse lesions, regeneration being assisted by the remarkable preservation of the reticulin framework which probably provides a scaffolding on which the lobule is reconstructed,

(ii) *continuous progress of the lesion leading to death with, at necropsy, the picture of acute or sub-acute liver necrosis,* may occasionally occur,

(iii) *development of liver cirrhosis* may result when the progress of the disease is more prolonged, fibrotic changes becoming predominant and giving rise to a picture of classical cirrhosis. Two such cases were encountered by the authors, one in a patient under arsenotherapy, the other in an elderly woman apparently suffering from epidemic hepatitis,

(iv) *mild residual fibrosis* may persist for some time in cases with the zonal type of lesion, probably recovering later.

There was no evidence of obstruction of the interlobular bile ducts, and the authors' material suggests that the pathological basis of epidemic jaundice is hepatitis, not biliary obstruction following duodenal inflammation.

The findings reported are particularly relevant to the question of the causation of the jaundice in arsphenamide-treated patients, as they show that the hepatic lesions differ in no essential details from those found in "serum jaundice" and in simple epidemic hepatitis ("catarrhal jaundice"). In one syphilitic patient, jaundice occurred before the administration of arsphenamide had been commenced, and in this man the same lesions were found as in the arsphenamide-treated cases. In one case of florid secondary syphilis without jaundice, no lesion was found in the specimen of liver obtained by biopsy. With reference to certain experimental data, the authors point out that these hepatic lesions of man are quite different from those produced in animals in arsphenamide poisoning. The latter are mainly hæmorrhagic, necrotic and fatty, and require massive doses for their production; the jaundice in man occurs with normal doses, and is characteristically irregular in its incidence.

The authors conclude that neither syphilitic lesions of the liver nor arsenobenzol poisoning cause the hepatitis seen in patients undergoing arsenical treatment. On the other hand, the identity of the histological lesions occurring in the course of arsenotherapy, in serum jaundice, and in "catarrhal jaundice" suggests that the cause may be identical in all three types.

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A NOTE ON SOME UNSUCCESSFUL ATTEMPTS TO DEMONSTRATE A VIRUS IN INFECTIVE HEPATITIS

by L. Hoyle, *Monthly Bulletin of the Ministry of Health and the Emergency Public Health Laboratory Service*, **2**, 99–101, October 1943

In this note from the *Emergency Public Health Laboratory* at Northampton, the author reports a small outbreak of mild infective hepatitis which attacked mainly children and young adults. Usually, there was a febrile pre-icteric phase of 2–3 days, followed by an afebrile icteric phase of 1–3 weeks. The incubation period appeared to be 3–4 weeks. One child died in the third week of the disease and showed extensive liver necrosis at *post-mortem.*

In the pre-icteric phase there was usually a mistaken diagnosis of influenza, which was a cause of difficulty in obtaining suitable material for isolation of the hypothetical virus.

The following materials were used in most of the author's studies:

(i) Blood serum, a frozen and thawed blood clot, from a child in the pre-icteric phase (2nd day of disease),

(ii) blood serum from a young adult taken on the 3rd day as jaundice was just beginning,

(iii) liver and spleen obtained at *post-mortem* from the fatal case (3rd week of disease),

(iv) nasopharyngeal washings from a young adult taken on the 1st day of jaundice (5th day of disease).

Intranasal, intraperitoneal and intracerebral inoculations of mice and guinea-pigs with these materials gave negative results, which were not unexpected but served to exclude leptospiral jaundice.

Attempts to demonstrate the presence of a virus by means of the complement-fixation reaction, using convalescent serum against (*a*) saline extracts of liver and spleen of the fatal case, and (*b*) heated serum of acute cases, were negative.

Negative results were also obtained from attempts to cultivate blood from acute cases (*a*) on the chorio-allantoic membrane of developing hen eggs, and (*b*) by the Maitland technique.

HEPATO-BILIARY FUNCTION

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A MODIFIED LÆVULOSE (FRUCTOSE) TOLERANCE TEST COMPARED WITH THE HIPPURIC ACID SYNTHESIS TEST OF HEPATIC EFFICIENCY

by J. B. Rennie, *British Journal of Experimental Pathology*, **24**, 26–32, February 1943

This work is a continuation of an investigation made at the *Gardiner Institute of Medicine* and the *Western Infirmary*, Glasgow (Rennie, 1942) into the efficiency of hippuric acid synthesis as a test of hepatic function. This test, originally devised by Quick (1936), involves the administration by mouth of 6 g. of benzoic acid. The urine passed during the succeeding 4 hours is collected and the hippuric acid in it is estimated gravimetrically, the results being expressed as grams of benzoic acid excreted in the 4-hour period. In 69

" normal controls " the range was 2·40–4·39 g. with a mean of 3·19 and a standard deviation of 1·07. In a study of 84 patients with disease of the liver the test was found to be of considerable value as an index of hepatic dysfunction. It proved useful in the prognosis of acute hepatitis but was of no help in the differential diagnosis of hepatic disease or jaundice.

The present paper deals with a series of 84 cases in which the results of the hippuric acid excretion and the lævulose tolerance tests of hepatic efficiency are compared. The lævulose tolerance test as described by Stewart, Scarborough & Davidson (1938) has been modified so that only two samples of blood are required—half and one hour respectively after the ingestion of 50 g. of lævulose by a fasting patient. Plasma lævulose was estimated directly by Herbert's (1939) method. In a series of 30 control cases the maximal rise in plasma lævulose varied between 3 and 12 mg. per 100 ml. and in two-thirds of the cases occurred in the one-hour specimen. A value of more than 15·0 mg. per 100 ml. of lævulose in the plasma in either of the specimens is considered abnormal. The shortened form of the lævulose tolerance test indicated impaired function of the liver in 44 out of 70 patients suffering from acute hepatitis, secondary carcinoma of the liver, obstructive jaundice and cirrhosis. This is a smaller proportion of positive results than was obtained by Stewart, Scarborough & Davidson who used the extended form of the test (four half-hourly specimens of blood) and estimated lævulose in whole blood. The test was negative in a high proportion of cases of secondary carcinoma of the liver and frequently also in obstructive jaundice. Biliary disease alone, with or without gall-stones, did not lower the lævulose tolerance and two cases of cholangitis gave results only just above normal. Raised plasma lævulose values were found most frequently in hepatic cirrhosis. In 9 out of 22 cases of acute infective hepatitis normal results were obtained but not all the patients were tested at an early stage of the disease.

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EXPERIMENTAL TRINITROTOLUENE POISONING: The Effect of Diet

by H. P. Himsworth and L. E. Glynn, *Clinical Science*, **4**, 421–443, December 1942

This paper from the Medical Unit and Department of Morbid Anatomy of *University College* Medical School, London, reports the influence of varying diets on the production in rats of toxic effects by trinitrotoluene. Both in the last and the present war it was recognised that workers in explosives factories who were exposed to trinitrotoluene were liable to develop severe liver necrosis and anæmia. Although the number of fatalities in proportion to the total number of workers exposed is relatively small, yet it has been found that mild symptoms of poisoning are present in 72% of workers and may cause considerable loss of working hours.

It has recently been shown that the degree of liver damage in animals exposed to various liver poisons varies considerably according to the nature of the diet, and in this paper the authors applied these methods to trinitrotoluene poisoning. The experiments were carefully controlled and consisted in feeding rats with three standard diets, one rich in protein, one rich in carbohydrate and the third rich in fats, and the test animals received in addition 0·15 g. of trinitrotoluene per kg. of body weight.

It was found that rats fed on the protein or carbohydrate diets failed to develop severe symptoms or pathological changes in the liver. In the protein-fed group there was no difference in the gain in weight from the controls. In the carbohydrate-fed group the normal increase in weight was suspended. In the rats on the fat diet, symptoms of poisoning essentially similar to those observed in man were noted—loss of weight, increased appetite, excretion of trinitrotoluene derivatives in the urine (rats excrete a pigmented derivative in the urine, whereas in man, dogs, cats, and rabbits the derivative is colourless but can be demonstrated by the application of Webster's Test), the development of a hæmolytic anæmia (in man an aplastic anæmia has been described, but this has not been reproduced with certainty in animals and was not observed in these experiments), and hepatic lesions varying from a fatty degeneration in the centre of the liver lobules to an acute necrosis of the liver cells. It was thought possible that, as trinitrotoluene is soluble in fat, the fat diet might facilitate absorption, but it was found that the poison was absorbed entirely in animals on all three diets. It was also found that animals which were on the fat diet before being given trinitrotoluene developed symptoms more rapidly than those which had been on a normal diet, and only started receiving the fat diet at the same time as the poison.

The authors consider that the high fat diet so influences the animal's metabolism that its ability to dispose of the trinitrotoluene within its tissues is impeded and toxic effects are thus facilitated. The natural inference may be drawn that some dietary control may limit the dangers to workers exposed to trinitrotoluene.

[*An excellent discussion on the history, clinical manifestations and pathology of trinitrotoluene poisoning was held at the Royal Society of Medicine, London, in April* 1942 (*Proc. roy. Soc. Med.*, 1942, **35**, 553). *The discussion was opened by Dr. J. C. Bridge* (*late H.M. Senior Medical Inspector of Factories of the Home Office*), *who described the history of the condition and gave official statistical information. Accounts of the actual working conditions and clinical symptoms were given by Dr. Catherine Swanston and Dr. Ronald E. Lane, both Medical Officers to factories. The pathological changes were described by Professor T. B. Davie, Professor of Pathology at the University of Liverpool.*]

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THE SPHINCTER MECHANISM OF THE LOWER END OF THE BILE DUCT

by G. Gordon-Taylor, *British Medical Journal*, **2**, 149–151, 8/8/42

This paper was read as the second and concluding part of a Hunterian Lecture delivered at the *Royal College of Surgeons of England.* It is generally agreed that some form of sphincteric mechanism exists at the lower end of the bile duct. Whether this sphincteric control is due to the muscular coats of the duodenum which the bile duct traverses in a peculiar oblique manner, or whether it is due to some special development of the muscular wall of the bile duct, is uncertain. Oddi (1887) claimed to have discovered a distinct circular band of fibres which has been called the sphincter of Oddi. Other observers claimed to have confirmed the presence of these fibres not only in man but in the dog and rabbit and also in the fœtus of the Antarctic whale. Some doubt has been cast on these observations, and Dardinkski (1934–35) denied the presence of an independent sphincteric ring. His conclusions have been confirmed by the present author's colleague, Professor John Kirk, who has made investigations on human adult and fœtal material. Boyden & Schwegler (1936, 1937) investigated the development of the muscular coats of the duct. They were of the opinion that these become differentiated *in situ* and were not of duodenal origin.

Both these observers, in common with Dardinkski and Kirk, mention the presence of longitudinal fibres which run down into the villous processes in the lower extra-duodenal part of the duct. Kirk and the present author consider that these fibres act as a retractor of the papilla. Retraction has been observed at operation in man and is followed by efflux of bile from the ostium. The muscular tissue in the villous processes around the ostium is of duodenal origin, and when it contracts it produces a clustering of these processes sufficient to prevent the regurgitation of duodenal contents into the bile duct. It would appear then that the sphincter of Oddi is in fact an artefact of dissection and that true circular fibres do not exist in the region investigated by Oddi.

This opinion is confirmed in some measure by the observations (reported in this paper) of Kirk, who showed that in the cat there is a thickening of the circular coat of the duodenum where the bile duct penetrates it, and that this thickening does not extend into the ampullary region. There are some suggestions from comparative studies that the ampulla is an involutionary structure which receives its muscular fibres from the duodenal musculature. These ampullary muscular fibres are, however, not circular in arrangement.

The experimental work on animals both with and without gall bladders has produced very equivocal results. The damage to nervous structures—ganglia and fibres—involved in some experiments is so extensive as to invalidate the conclusions drawn from the observations. In man, many relevant observations have been made which indicate that the sphincteric mechanism is not only efficient but is sensitive to the reaction of the bile and its concentration. When this mechanism is damaged at operation cholangitis is an almost constant sequel. It is significant that cholangitis is absent in cases of congenital dilatation of the bile duct treated by anastomosis of the dilated bile passages and the duodenum (Walton, 1939). The explanation of such immunity may be that some bile finds its way through the normal ostium and so prevents any possible regurgitation of duodenal contents in the bile duct.

The present author lays no claim to have solved the problem of the control of the biliary secretion into the duodenum. His paper is in many ways a challenge to surgeons to make more careful observations when opportunities present themselves to see the biliary ostium in action. It may well be that quite apart from controlling the flow of bile into the duodenum and preventing the reflux of duodenal contents into the bile ducts, the sphincteric mechanism may also include some chemo-receptor mechanisms, the nature of which is indicated by a recent paper by Long (1942).

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EFFECT OF DIET ON THE CONCENTRATION OF CHLOLESTEROL IN BLOOD AND BILE

by N. Gough, *British Medical Journal*, **2**, 390–391, 25/9/43

In this paper from the Clinical Laboratory of the *Royal Infirmary*, Edinburgh, the author reports an investigation into the relationship between high and low cholesterol diets and blood cholesterol. Hospital patients with apparently normal metabolism were fed on low-cholesterol diets (about 300 mg. daily) for a fortnight, after which they were given an additional 900 mg. of pure cholesterol, or 3 eggs (approximately 1,100 mg. of pure cholesterol) or 50 g. of sheep's brain (approximately 2,170 mg. cholesterol) daily. Blood cholesterol was estimated at intervals of 3 days, and at the same time every day, throughout the experiments.

Estimated by Myer & Wardell's colorimetric method, plasma cholesterol was unaffected by diet in 8 out of 10 cases, while in 2 cases it was raised by the addition of 900 mg. of cholesterol daily to the basic diet, and also by the daily addition of 3 eggs. In a second series of 10 cases plasma cholesterol, estimated by Okey's digitonin precipitation method, did not rise with a high-cholesterol diet.

Single doses of 5 g. of crystalline cholesterol by mouth in 4 normal subjects did not raise either the free or the esterified cholesterol in blood, as estimated by Okey's method. This may be due to a failure in absorption of crystalline cholesterol or to some mechanism whereby it is removed from the blood and altered into some compound not detected by the analytical method employed.

After 2 or 3 days on a low-cholesterol diet, 10 patients with biliary fistulæ were given a diet with a high content of cholesterol, either as the pure substance or as brain. Bile was collected from the fistula on alternate days. The cholesterol content of the bile was very low immediately after operation, but rose gradually, although with considerable day-to-day variation (10–45 mg. per 100 cm.^{3}). As in human cases of biliary fistula it is impossible to determine what proportion of the bile is draining externally and what is draining through the common bile duct, the total secretion of bile or cholesterol cannot be estimated, but the concentration of cholesterol in a given sample of bile can be compared with the cholesterol ingested in the diet. Of these 10 cases, 1 showed a distinct rise in bile cholesterol concentration on a diet containing about 2,000 mg. of cholesterol (50 g. of sheep's brain) daily, 1 a rise when the high-cholesterol diet was first given, with a subsequent return to the original level while the patient was still on the high-cholesterol diet, and 2 a fall in the cholesterol concentration in the bile on a low cholesterol diet. In the remaining 6, bile cholesterol concentration did not vary with changes in the cholesterol content of the diet.

To overcome the difficulty of determining the total output of cholesterol in the bile, a tube was inserted into the common duct of a dog so that all the bile drained externally, and the animal was given 1 g. of sodium taurocholate by mouth daily to compensate for the absence of bile in the intestine. After about 10 days the volume and cholesterol content of bile became fairly constant (13–14 mg. of cholesterol per 100 cm.^{3} bile, and total bile cholesterol excreted about 20 mg. daily). Feeding of 50 g. of sheep's brain (approximately 2 g. cholesterol) then produced an immediate rise in bile cholesterol concentration (27 mg. per 100 cm.^{3} and total bile cholesterol 38 mg.) which lasted for 48 hours. Subsequently, however, both concentration and total output of cholesterol in the bile returned to the original level, although the high-cholesterol diet was maintained.

The author concludes that there is no direct correlation between the intake of cholesterol and its level in the blood and bile and, consequently, that there is no ground for prohibiting foods rich in cholesterol from the diet of patients with cholecystitis and cholelithiasis.

KIDNEY IN HEALTH AND DISEASE

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THE SECRETION OF URINE BY DEHYDRATED AND NORMAL INFANTS

by W. F. Young & R. A. McCance, *Archives of Disease in Childhood*, **17**, 65–81, June 1942

Gastroenteritis is necessarily a subject of considerable interest to all those responsible for the care of infants. The chemistry of the blood serum in this condition has been carefully investigated, and a few authors have carried out urine and renal function tests. It has recently been shown (McCance & Young, 1941) that the kidneys of new-born infants function differently from those of adults.

In the present investigation, renal function was studied in 41 infants admitted to a gastroenteritis ward of a children's hospital and 20 normal infants who were convalescent. Although it has been shown that above the age of one year the excretion of urea and other functions of the kidney are proportional to the surface area of the body, the authors demonstrate that this relationship does not hold in infancy, and that at birth the clearances of urea and minerals are lower than in adult life. They are particularly low in premature infants, but increase with age during the first year. The urine of an infant tends to have a low specific gravity even when very little is being passed. Further investigations have shown that, judged by adult standards, the glomerular filtration rates (measured by the inulin clearances) are lower in infancy and that they tend to fall when the volumes of urine diminish. These findings together indicate that the efficiency of an infant's kidneys depends upon the maintenance of a high rate of urine flow.

In infants who are dehydrated the output of urine is reduced and this is inevitably accompanied by functional renal failure. This accounts for some of the gross changes in the serum chemistry which have been described in infants suffering from gastroenteritis. Such changes may be exaggerated by misguided treatment. For instance, young infants seldom eliminate urine as concentrated as normal saline and therefore indiscriminate administration of such a fluid may raise the serum sodium and chloride to dangerously high levels. It may be an essential part of treatment to replace minerals lost in the stools and vomit, but therapy of this sort should be carefully controlled.

No evidence of any specific renal lesion has been found in dehydrated infants. Their kidneys are functioning in the normal infantile manner, but when the amount of water available for excretion is diminished, they may be unable to maintain a constant internal milieu.

The authors' findings are given in detail in the original paper. The chemical estimations were made as described by McCance & Young (1941), and Young, Hallum & McCance (1941).

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ABSORPTION AND EXCRETION OF OXALATE

by J. F. Barrett, *Lancet*, 2, 574–575, 14/11/42

Clinical interest in oxalate metabolism depends mainly on the presence of calcium oxalate in renal calculi and on the excretion of calcium oxalate crystals in urine. The crystals are often viewed with suspicion as possible precursors of calculi. In this paper from the *Courtauld Institute of Biochemistry*, Middlesex Hospital, the author reports an investigation carried out with the above considerations in mind on the factors influencing the absorption and excretion of oxalate.

The ester method of Dodds & Gallimore (1932) was employed for the determination of oxalate. The normal urinary output for fourteen normal adults on an uncontrolled diet was found to be 20–47 mg. of oxalate per day, with an average of 33 mg. per day. The output in two cases was shown to remain steady over a period of several days on a constant diet. The effect of consuming 150–200 g. rhubarb was studied in three human subjects. In these cases the daily urinary output of oxalate rose to almost twice the normal figure.

If, however, the meal at which the rhubarb was eaten was supplemented by ½ pint [about 285 cm.³] of milk, or in one case, by 0·4 g. calcium chloride, the daily excretion of oxalate remained within normal limits. This effect was attributed to the conversion of soluble oxalate into the almost insoluble calcium oxalate in the intestine. Experiments on a human subject as well as on a cat showed that calcium oxalate was poorly absorbed.

The authors suggest that milk should be taken with foodstuffs such as rhubarb and spinach which are rich in soluble oxalates, in order to avoid excessive oxalate absorption. In this way the kidneys are saved the task of excreting the absorbed oxalate, which if present in large quantity may favour the formation of stones.

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ATHEROSCLEROSIS OF THE MAIN RENAL ARTERIES IN ESSENTIAL HYPERTENSION

by G. O. Richardson, *Journal of Pathology and Bacteriology*, 55, 33–39, January 1943

This paper, from the Department of Pathology of the *Royal Victoria Infirmary*, Newcastle-on-Tyne, describes an investigation into the incidence of lesions of the renal arteries in essential hypertension.

Since Goldblatt and his associates described, in 1934, a persistent hypertension in dogs in which renal ischæmia had been induced by clamping the main renal vessels, investigations have been proceeding in an endeavour to find changes in cases of human hypertension of comparable nature. A few cases of hypertension in children and young adults have been relieved by the excision of a chronic pyelonephritic kidney, and there have been isolated accounts in which a thrombosis of the renal arteries was associated with hypertension, but no consistent lesion had been described in classical cases of " essential hypertension."

In this study the author examined the kidneys and renal vessels in a series of 145 patients who had died between the ages of 20 and 80. There were 32 cases of hypertension (as judged by a blood pressure reading in life of at least 150/90 mm. Hg or, where a blood pressure reading was not available, by a heart with idiopathic left ventricular hypertrophy and weighing more than 400 grams in the female or 450 grams in the male). The control series of 113 cases were of comparable ages but without clinical evidence of hypertension or *post mortem* evidence of cardiac hypertrophy.

In 25 of the 32 hypertensive cases there was apparent stenosis of one or both renal arteries by atheromatous plaques. In the majority of these cases the narrowing was at the proximal portion of the artery, near its origin from the aorta. Beyond this region the renal artery and its branches were natural, although the kidneys showed macroscopic and microscopic lesions characteristic of essential hypertension (arteriolar sclerosis). In the remaining 7 hypertensive cases, no lesion was found in either renal artery, but there is no report of the changes in the kidney itself. Of the 25 cases with hypertension and stenosis of the renal artery, 8 showed generalised atherosclerosis of all the vessels, in 12 the atheroma was limited to the aorta, and in the remaining 5 the atheromatous lesions were virtually limited to the renal arteries.

In the control group of 113 cases without hypertension 105 showed no lesions in the main renal arteries. In the remaining 8 cases, atheromatous plaques were present, but in only 3 was the degree of occlusion comparable with that seen in the hypertensive cases.

The importance of this study is that it produces rational morphological evidence for the initiating step in the vicious circle of essential hypertension of man. There is no precise knowledge as to the factors which induce atheroma of the aorta and its main branches, but it is clearly a degenerative lesion and occurs with increasing severity as age advances. It has long been recognised that atheromatosis is commonly more severe in cases of hypertension but may, and frequently does, occur without the presence of hypertension. This paper shows that, in the majority of a series of cases of hypertension, there is narrowing of the renal arteries by atherosclerosis of a degree likely to produce some renal ischæmia in life and to initiate the changes in the renal parenchyma which are associated with hypertension.

[*Note by Reviewer:* Interest has recently been focussed on the specialised muscle cells of the juxtaglomerular complex, or Goormaghtigh cells, which occur in the walls of afferent renal arterioles at the commencement of the glomerulus; it has been shown that there is a hyperplasia of these cells in hypertension in man and animals, and they have been suggested as the source of a vasopressor substance. A good review of these cells and their significance in renal pathology will be found in a paper by McManus (1942).

The fact that, in 25% of the cases of hypertension in Richardson's series, no lesion was found in the renal arteries does not detract from the significance of the findings, for it is already known that there are many other modes by which renal ischæmia or hypertension may occur. It is perhaps unfortunate that a description of the changes in the kidneys in this group was not included. Nor is it surprising that, in under 3% of the controls, stenotic lesions were found in the renal arteries without evidence of hypertension. In experimental animals the degree of ischæmia has to be adjusted very carefully to induce hypertension, which, even under these circumstances, may not develop in some of the animals.

It is clear that studies of larger series of cases on the lines carried out by Richardson are necessary before this evidence can be accepted without reservation, but, apart from its academic interest, it does point a way to a possible form of therapy in early cases of hypertension. Byrom & Wilson (1941) of the Medical Unit of the *London* Hospital showed that when hypertension has been induced in experimental animals and allowed to persist, removal of the constricting mechanism does not relieve the hypertension, as secondary irreversible lesions have developed in the kidneys themselves. If an anastomosis between the kidney and the omentum were produced surgically, it might, in early cases, overcome the renal ischæmia consequent on the stenosis of the renal artery. Indeed there are already claims of promising results from such an operation.]

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TREATMENT OF THE NEPHROTIC SYNDROME WITH SERUM TRANSFUSIONS

by H. Brown, C. H. Gray & P. L. Mollison, *British Medical Journal*, 1, 515–518, 25/4/42

This paper is the text of a report to the *Medical Research Council* from two London Blood Supply Depots. The administration of a diet rich in protein to patients affected

with the nephrotic syndrome has for long been accepted as a rational treatment. The results, however, are frequently disappointing, because it proves difficult in practice to influence the level of the plasma proteins. Now that human serum and plasma have become available in large quantities for transfusion purposes, it is natural that an attempt should be made to see whether more satisfactory results can be achieved by the administration of protein intravenously. Recent work by Madden & Whipple (1940) has shown, however, that protein introduced intravenously can leave the bloodstream rapidly so that there is no guarantee that even a temporary increase in the plasma protein level can be produced by this method.

The first report upon the results of treatment of cases of nephrosis with serum transfusions was very encouraging (Aldrich, Stokes, Killingsworth & McGuinness, 1938), 6 out of 9 cases being completely relieved of œdema, but the experience of Weech, Goettsch & Lyttle (1940) was very different, only 1 out of their series of 7 cases responding favourably.

The present authors, working in the *Emergency Blood Transfusion Service* established by the *Medical Research Council* in the London area, have carried out investigations in an attempt to obtain further data upon the value of serum transfusions in the treatment of nephrotic syndrome. Like Aldrich *et al.* they used 4-times concentrated serum, reconstituted from the dried (lyophile) product. Their subjects were not closely comparable with those of Aldrich, however, for whereas the latter were mainly children affected with lipoid nephrosis, 8 out of 12 of the present authors' cases were adults who were in the nephrotic stage of chronic glomerulo-nephritis. In these cases it was naturally not hoped that improvement would be other than temporary. In the remaining 4 cases treated, the diagnosis was amyloid nephrosis and lipoid nephrosis in 2, and malabsorption of protein from the alimentary tract in the other 2.

Most of the patients received two or more transfusions, and the dosage ranged from 50 to 500 cm.^{3} of the 4-times concentrated serum. When amounts up to 200 cm.^{3} were transfused, the time taken for transfusion was less than 30 minutes; when larger amounts were administered, up to 8 hours was taken. No serious symptoms developed during the transfusions, although some febrile reactions occurred.

Of 11 œdematous patients only 2 were completely relieved of their œdema following transfusion and in one of these the œdema had returned within 10 days and was then unaffected by a further transfusion. In 2 cases there was a slight improvement and in 2 cases there was an increase in the œdema. In the remaining 5 cases no change occurred.

Investigations showed a fall in hæmoglobin concentration and in hæmatocrit immediately after transfusion, with an increase in serum protein concentration. The hæmoglobin concentration and hæmatocrit had risen again 24–48 hours later, and the serum protein concentration had in the majority of cases fallen to the pre-transfusion level. From their available data the authors conclude that the "lost protein" is not excreted in the urine but is taken up by the tissues. They consider that failure to obtain a good diuresis after transfusion is partly to be explained by the large amount of salt contained in a dose of concentrated serum and they believe that serum transfusions are likely to prove of little value in the treatment of the nephrotic syndrome, at least when the amount of protein transfused is from 20 to 100 grams.

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